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(54) Title: PRODRUGS CONTAINING NOVEL BIO-CLEAVABLE LINKERS

(57) Abstract: The invention provides the compounds of formula (I) or pharmaceutically acceptable salts thereof. The invention also provides pharmaceutical compositions comprising one or more compounds of formula (I) or intermediates thereof and one more of pharmaceutically acceptable carriers, vehicles or diluents. The invention further provides methods of preparation and methods of use of prodrugs including NO-releasing prodrugs, double prodrugs and mutual prodrugs comprising the compounds of formula (I).



WO 2006/027711 A2

PRODRUGS CONTAINING NOVEL BIO-CLEAVABLE LINKERS

This application takes priority from US Provisional Application USSN: 60/604,632 filed 26 August 2004 and Indian Provisional Application 779/MUM/2005 filed 01 July 2005 and are herein incorporated in their entirety.

Field of the Invention

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The present invention relates to compositions of prodrugs, including NO-releasing prodrugs, codrugs, double prodrugs and mutual prodrugs, containing bio-labile linkers and linkages, processes for their preparation and pharmaceutical compositions containing them and their use.

Background of the Invention

A prodrug is an active drug chemically transformed into a *per se* inactive derivative which by virtue of chemical or enzymatic attack is converted to the parent drug within the body before or after reaching the site of action. The process of converting an active drug into inactive form is called drug latentiation. Prodrugs can be carrier-linked-prodrugs and bioprecursors. The carrier-linked prodrug results from a temporary linkage of the active molecule with a transport moiety. Such prodrugs are less active or inactive compared to the parent active drug. The transport moiety will be chosen for its non-toxicity and its ability to ensure the release of the active principle with efficient kinetics. Whereas the bioprecursors result from a molecular modification of the active principle itself by generation of a new molecule that is capable of being a substrate to the metabolizing enzymes releasing the active principle as a metabolite.

Prodrugs are prepared to alter the drug pharmacokinetics, improve stability and solubility, decrease toxicity, increase specificity, and increase duration of the pharmacological effect of the drug. By altering pharmacokinetics the drug bioavailability is increased by increasing absorption, distribution, biotransformation, and excretion of the drug. Limited intestinal absorption, distribution, fast metabolism, and toxicity are some of the causes of failure of drug candidates during development. Avoidance of the foreseeable or proven pharmacokinetic defects thus assumes considerable significance in drug research. Accordingly, prodrugs play a significant role in drug research as well.

In designing the prodrugs, it is important to consider the following factors: a) the linkage between the carrier and the drug is usually a covalent bond, b) the prodrug is inactive or less active than the active principle, c) the prodrug synthesis should not be expensive, d) the prodrug has to be reversible or bioreversible derivative of the drug, and e) the carrier moiety must be non-toxic and inactive when released.

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Prodrugs are usually prepared by: a) formation of ester, hemiesters, carbonate esters, nitrate esters, amides, hydroxamic acids, carbamates, imines, mannich bases, and enamines of the active drug, b) functionalizing the drug with azo, glycoside, peptide, and ether functional groups, c) use of polymers, salts, complexes, phosphoramides, acetals, hemiacetals, and ketal forms of the drug. For example, see Andrejus Korolkovas's, "Essentials of Medicinal Chemistry", pp. 97-118.

The discovery and characterization of endothelium-derived nitric oxide (NO) was the subject of the 1998 Nobel Prize in Medicine and Physiology. NO is a major signaling molecule with important biological roles. See, for example, Kerwin, Jr., J. F. et al., J. Med. Chem. 1995, 38, 4343, and Williams, R. J. P., Chem. Soc. Rev., 1996, 77. The major biological functions of NO include controlling blood pressure, smoothing muscle tone and inhibition of platelet adherence and aggregation, assisting the immune system in destroying tumor cells and intracellular pathogens and participating in neuronal synaptic transmission. See, for example, Moncada, S. et al., Pharmacol. Rev. 1991, 43, 109; Bredt, D.S. et al., Anuu. Rev. Biochem., 1994, 63, 175; Schmidt, H. H. W. et al., Cell 1994, 78, 919; Feldman, P. L. et al., Chem. and Eng. News. 1993, 71 (20th December issue), 26; and Wilsonm E. K., Chem. and Eng. News. 2004 (8th March issue), 39. Endogenously, NO is produced from arginine by the catalytic action of nitric oxide synthase. See, for example, Nathan, C. et al., Cell 1994, 78, 915, and Marietta, M. A., Cell 1994, 78, 927.

NO is a free radical as well as a scavenger of free radicals. NO reacts quickly with ubiquitously generated reactive oxygen species (ROS) such as superoxide (O₂⁻) to generate a nefarious peroxynitrite (ONOO⁻) molecule, which is implicated in many human diseases such as diabetes, heart disease, Alzheimer's disease and multiple sclerosis. In this setting, NO is often viewed as pathogenic. However, the chemistry of NO can also be a significant factor in lessening the injury mediated by reactive oxygen species (ROS) and reactive nitrogen oxide species (RNOS). There is a relationship

between NO and oxidation, nitrosation and nitration reactions. A number of factors determine whether NO promotes, abates or interconnects these chemistries. See, for example, Espay, et al., A chemical perspective on the interplay between NO, reactive oxygen species, and reactive nitrogen oxide species, Ann N. Y. Acad. Sci. 2002, 962, 195.

Thus, by being a free radical, along with the ability to scavenge other free radicals, NO is placed in a pivotal regulatory position. Insight into these pathophysiological processes and signaling are highly relevant to develop therapeutics.

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NO-DONORS:

NO deficiency has been implicated in the genesis and evolution of several disease states. In patients with cardiovascular problems, the production of superoxide is increased and level or location of NO synthesis is disrupted thereby causing cellular dysfunction as a result of vasoconstriction of blood vessels, which can lead to, if prolonged, cell damage or death. Agents that act to maintain the normal balance between NO and superoxide in vascular endothelial cells may prove particularly useful in this regard. See, for example, Stokes, K., et al., Free Radic. Bio. Med., 2002, 33, 1026-1036.

. Nutritional and pharmacological therapies that enhance the bioactivity or production of NO have been shown to improve endothelium-dependent vasodilation, reduce symptoms, and slow the progression of atherosclerosis. Some of the strategies for NO modulation encompass anti-inflammatory, sexual dysfunction, and cardiovascular indications. Apart from newly developed drugs, several commonly used cardiovascular drugs exert their beneficial action, at least in part, by modulating the NO pathway. Pharmacological compounds that release NO have been useful tools for evaluating the pivotal role of NO in cardiovascular physiology and therapeutics.

There are a wide variety of structurally dissimilar organic compounds that act as NO donors and release NO in solution. Some NO donors, such as isoamyl nitrite, nitroglycerine (GTN) and sodium nitroprusside, have been used in cardiovascular medicine long before their biochemical mechanism was understood. The common mode of action for these drugs is liberation of NO, which evokes relaxation of smooth muscle through activation of guanylate cyclase with subsequent formation of cGMP. The relative importance of enzymatic versus non-enzymatic pathways for NO release, the identity of

the actual NO-generating enzymes and the existence of competing metabolic events are additional important determinants of the different NO donor classes. Pharmacological compounds that release NO constitute two broad classes of compounds: those that release NO or one of its redox congeners spontaneously and those that require enzymatic metabolism to generate NO. See, for example, Ignarro, L. J. et al., Nitric oxide donors and cardiovascular agents modulating the bioactivity of nitric oxide: an overview, Circ. Res. 2002, 90, 21-28.

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Nitroglycerine/glycerine trinitrate (GTN) and compounds referred to as nitrovasodilators or NO donors are frequently used in the treatment of ischemic heart disease. The common mode of action for these drugs is liberation of NO, which evokes relaxation of smooth muscle through activation of guanylate cyclase with subsequent formation of cGMP. However, early development of tolerance to nitrate therapy, particularly during acute myocardial infarction, has been the clinically significant drawback with GTN and some of the other available organic nitrates. This is a significant clinical problem and there exists a need for novel nitrate-based anti-anginal agents, which do not cause the problem of nitrate tolerance.

There are a number of new examples of organic nitrates in which an alkyl or aralkyl mononitrate is covalently linked to an existing drug molecule. Existing drugs from a large number of therapeutic areas such as anti-inflammatory, antiallergic, antihypertensive, antibiotic, anticancer, antidiabetic, antiviral, antianginal, anticonvulsant, analgesic, antiasthmatic, antidepressant, antidiarrheal, antiinfective, antimigraine, antipsychotic, antipyratic, antiulcerative, antithrombotic, etc., were madeand evaluated. Some of Nicox's patents include: Synthesis and evaluation of nitrooxy derivatives of NSAIDs (WO 9412463, WO 0230867, WO 0292072, WO 0313499 and WO 0384550), aspirin (WO 9716405, WO 0044705 and WO 0104082), paracetamol (WO 0112584 and WO 0230866), antiepileptic agents (WO 0300642 and WO 0300643), COX-2 inhibitors (WO 0400781 and WO 0400300), statins (WO 04105754), ACE inhibitors (WO 041 10432 and WO 04106300), and of known drugs used for the treatment of disease conditions resulting from oxidative stress and endothelial dysfunction (WO 0061537).

Most of these nitrate esters were shown to possess not only superior or equal efficacy when compared to the original drug but also exhibit much-reduced side effects. In fact, because of their superior efficacy combined with reduced toxicity, a few of such nitrate ester-containing drug conjugates are successfully passing through various stages of clinical trials. Some of Nicox's nitrooxy derivatives of drugs which are in clinical trials include: NCX 4016 (Phase II, peripheral vascular diseases), NCX 701 (Phase II, Acute pain), HCT 1026 (Phase I, Alzheimer's disease), HCT 3012 (Phase II, Osteoarthritis), NCX 285 (IND, Osteoarthritis), NCX 1022 (Phase Ha completed, Dermatitis), NCX 1020 (Phase I, Asthma/COPD), NCX 1000 (Phase I, Portal hypertension), and NCX 1510 (Phase II, Allergic rhinitis).

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US5767134 and US20050002942A1 disclosed a few disulfide-containing prodrugs/folate-drug conjugates. WO 9842661, US 5807847, WO 0054756 and WO 0149275 reported a few nitrooxy derivatives of organic molecules containing sulfahydryl or disulfide group which are called "SS-nitrates". These references are incorporated herein by reference.

Representative examples from WO 9842661 have shown superior vasorelaxant activity and no tolerance was observed to the cGMP-increasing effects of those compounds under the same experimental conditions used for the induction of in vivo tolerance. WO 0149275 reports drug conjugates where an anti-inflammatory drug is covalently linked to the betø-mercapto-nitrate via thioester bond. Biotransformation pathways proposed for NO release from GTN have largely been heme-dependent or sulfahydryl-dependent. See, for examples, Thatcher, G. R. J. et al., Chem.Soc. Rev. 1998, 27, 331 and reference cited therein, and Bennett, B M. et al., Trends Pharmacol, Sci. 1994, 15, 245. These references are incorporated herein by reference.

A mutual prodrug is the association in a unique molecule of two drugs, usually synergistic, attached to each other, one drug being the carrier for the other and vice versa. The embodiments of the invention also provide mutual prodrugs, which are prodrugs of two or three therapeutic agents currently used/potential for use in combination therapy utilizing novel bio-cleavable linkers, water-soluble prodrugs of insoluble/sparingly-soluble therapeutic agents using the same linker technology and water-soluble double and

triple prodrugs of sparingly-soluble therapeutic agents or any of the prodrugs linked to NO-releasing agent using the same linker technology.

Summary of the Invention

Present invention relates to the compounds of formula (I) or pharmaceutically acceptable salts thereof:

$$D^{1} \stackrel{L^{1}}{=} A \stackrel{A}{=} B \stackrel{A^{1}}{=} \left(\stackrel{L}{=} A^{1} \stackrel{A}{=} A \stackrel{L^{2}}{=} D^{2} \right)$$
Formula (I)

wherein,

10 a is 0-2;

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B independently represents a bond, $(CH_2)_b$, $(CH_2CH_2O)_C$ S-S, S-S=O, S-SO₂ or S-S=NH; b is 1-6; c is 1-1000;

A and A¹ independently represent a bond, (CH₂)a, 1,2-phenylene, 1,3-phenylene or 1,4-phenylene;

15 d is 1-8;

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D¹ represents a therapeutic agent comprising one or more of the functional groups selected from the group consisting of -OH, -SH, -NHR¹, -CO₂H, -CONHR¹, - OC(=O)NHR\ -SO₂NHR¹, -OSO₂NHR¹, -N(R^CC=O)NHR¹ and -N(R^SO₂NHR¹; D² independently represents D¹, a peptide, protein, monoclonal antibody, vitamin, R², R³,

20 R⁴, NO, NO₂, a linkable nitric oxide-releasing group comprising a NONOate, a group comprising one or more of water-solubilizing functional groups, or a polymer; E independently represents CH₂ or a bond;

L¹ and L² independently represent a bond, O, S, NR¹, L, or a linkage selected from the group consisting of:

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L is R ¹² or a group with bonding in any direction, independently selected from the group consisting of:

X independently represents a bond, C, O, S, or NR1;

Y independently represents a bond, C=O, C=S, S=O, SO₂, PC=O)XR¹, or (CH₂)a;

Z independently represents a bond, or (CH₂)J; wherein, j is 1-4;

10 R¹ independently represents a bond, H, (C₁-Cs)alkyl, (Cs-Cu)SIyI, aralkyl or M⁶⁺;

R² independently represents H, NH₂, or NHAc;

R³ independently represents H, CO₂R⁵, CH₂CO₂R⁵,

R⁴ independently represents H, OH, 0-(Ci-C ₈)alkyl, 0 M^{c+}, or a group selected from the group consisting of:

$$CO_{2}R^{6}$$

$$CH_{2}CO_{2}R^{6}$$

$$CO_{2}R^{6}$$

$$CO_{2}R^{6}$$

$$CO_{2}R^{6}$$

$$CO_{2}R^{6}$$

$$CO_{2}R^{6}$$

$$CO_{2}R^{6}$$

$$R^{10}$$

$$R$$

M independently represents Na, K or a pharmaceutically acceptable metal ion,

6 = 1-3

 $\rm R^5$ independently represents at each occurrence H, Me+, (Ci-C₈)alkyl, (C₃-Cs)cycloalkyl, substituted (C₅-Ci₄)aryl, hetero(C₂-C₁₄)aryl, C(=O)(CH₂)_fCHR⁹CO₂R⁵; CH₂C(=O)OR⁵, P(=O)(OR⁵)₂,

$$CO_2R^6$$
, $CH_2CO_2R^6$, CO_2R^6 , CO_2R

X² independently represents O, S, SO, SO₂, or NR⁵;

 R^6 independently represents H, Na^+ , K^+ , any other pharmaceutically acceptable metal ion, $(Ci-C_8)$ alkyl, or (C_3-C_8) cycloalkyl,

R⁷ independently represents at each occurrence same or different R⁵;

5 R⁸ independently represents CH₂, O, NR⁴, S, S=O or O=S=O;

R⁹ independently represents H, (Ci-C₈)alkyl or an amino acid;

f is 0-6;

g is 0-1;

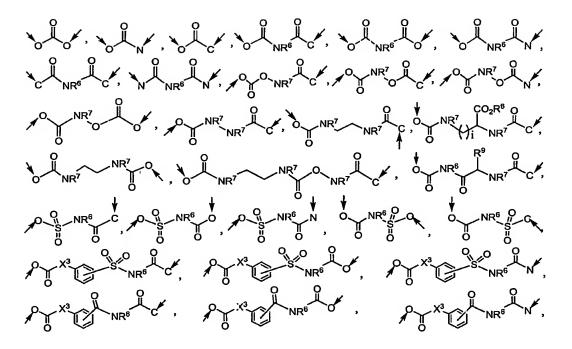
his 1-2000;

10 i is 1-4;

 R^{10} and R^{11} independently represent H, (Ci-C₈)alkyl, (C₃-C₈)cycloalkyl, or a group selected from the group consisting of:

with a proviso that when R^{10} is selected from the above group, R^{11} represents H or (C₁-C₈)alkyl, and when R^{11} is selected from the above group, R^{10} represents H or (Ci-C₈)alkyl;

5 R¹² independently represents a group selected from the group consisting of:



5 and X^3 is independently O or NR⁷.

Another embodiment of the invention is a pharmaceutical composition comprising one or more compounds of formula I or intermediates thereof and one more

of pharmaceutically acceptable carriers, vehicles or diluents. Further embodiments include methods of preparation and methods of use of prodrugs including NO-releasing prodrugs, double prodrugs and mutual prodrugs comprising the compounds of formula I.

Detailed Description of the Invention

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The present invention characterizes compositions, methods of preparation and methods of use of prodrugs, NO-releasing prodrugs, mutual prodrugs, double prodrugs, and codrugs.

The compounds of the present invention are prodrugs or mutual prodrugs in which known therapeutic agents or potential therapeutic agents are linked covalently to novel biocleavable linkers.

The compounds of the present invention also include NO-releasing prodrugs in which a therapeutic agent is linked covalently to nitrooxy (nitrate ester) group via a novel bio-cleavable linker containing a strategically placed disulfide group at β -position to the nitrate ester. The present invention also characterizes composition of NO-releasing prodrugs (i.e., nitrooxy ester or nitrate ester prodrugs), processes for their preparation, pharmaceutical composition containing them and their use.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Listed below are definitions of various terms used to describe the compounds of the present invention. These definitions apply to the term as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or part of a larger group.

The term "amino-containing" refers to drug/carrier molecule with NH functional groups such as amino (both primary and secondary), amide, urea, sulfonamide, carbamate, phosphoramadite, sulfamate, hydrazone, semicarbazone, thiosemicarbazone, hydrazide, carbazate and the like. This also includes NH-containing heterocylic compounds such as imidazoles, benzimidazoles, pyrazoles, benzpyrazols, pyrrols, indoles, triazoles, tetrazoles, benzotriazoles, benzotetrazoles and their derivatives. These NH-containing heterocyclic compounds can be sub-structures of more complex drug/carrier molecules. Amino group of the candidate drug can be primary or secondary (both acyclic and cyclic) which include amide-NH, sulfonamide-NH, carbamate-NH,

sulfamate-NH, hydrazide-NH, hydrazone-NH, semicarbazone-NH, thiosemicarbazone-NH, urea-NH and also drugs containing indole, imidazole, benzimidazole, thiazole, oxozole, pyrrole, pyrazole, triazole, tetrazole, or similar NH-containing heterocylic substructures of a more complex drug molecule.

The term "hydroxyl-containing" refers to drug/carrier molecules with hydroxyl groups (primary, secondary and tertiary) including hydroxyl groups of hydroxamic acids and ketoximes derived from keto-containing molecules. Hydroxyl group of drugs can be of primary, secondary or tertiary nature.

The term "sulfahydryl-containing" refers to drug/carrier with free sulfahydryl 10 (SH) group.

The term "halo" refers to fluoro, chloro, bromo, and iodo.

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The term "halide" refers to fluoride, chloride, bromide, and iodide.

The term "alkyl" refers to acyclic alkyl chains. For example, the term ${}^{"}C_1-C_8$ alkyl" refers to methyl, ethyl, propyl, isopropyl, butyl, cyclobutyl, s-butyl, and t-butyl, pentyl, hexyl, heptyl, octyl, and the like.

The term "cycloalkyl" refers to cyclic alkyl chains, e.g., the term ${}^{\circ}C_3 - C_8$ cycloalkyl" refers to cyclopropyl, cyclooctyl, cyclopentyl, cyclohexyl, cyclohexyl, cyclohexyl, cyclooctyl and the like.

The term "aryl" refers to phenyl, naphthyl and the like.

The term "aralkyl" refers to benzyl, phenethyl and the like.

The term "alkoxy" refers to both acyclic and cyclic Ci-C₈ alkyloxy. For example, the term "Ci-C₈ alkyloxy" refers to methoxy, ethoxy, propoxy, isopropoxy, cyclopropoxy, butoxy, cyclobutoxy, s-butoxy, and t-butoxy, cyclopentyloxy, pentyloxy, hexyloxy, cyclohexyloxy, heptyloxy, cycloheptyloxy, octyloxy, cyclooctyloxy and the like.

The term "heterocyclic" and "heteroaryl" refers to both saturated and unsaturated 5- and 6-membered rings (including benzo-fused) containing from 1 to 4 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. All of these rings may be substituted with up to three substituents independently selected from the group consisting of amino, halo, alkoxy, alkyl, cyano, nitro, hydroxyl, sulfahydryl, carboxyl and the like, Saturated rings include, for example, pyrrolidinyl, piperidinyl, piperazinyl,

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tetrahydrofiiryl, oxazolidinyl, dioxanyl, pyranyl, and the like. Benzofused saturated rings include indolinyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl and the like. Unsaturated rings include furyl, thienyl, pyridinyl, pyrrolyl, N-methylpyrrolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, tetrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, and the like. Benzofused unsaturated rings include isoquinolinyl, benzoxazolyl, benzthiazolyl, quinolinyl, benzofuranyl, thionaphthyl, indolyl and the like.

The term "substituted alkyl" refers to acylic and cyclic alkyl groups substituted with one or more of groups such as alkyl, aryl, hydroxy, alkoxy, cyano, carboxyl, sulfahydryl, alkylthio, amino, nitro, halo, carbonyl, carbamato, sulfamato, sulfanato, sulfato, and the like.

The term "substituted aryl" refers to aryl groups substituted (including fused) with one or more of groups such as alkyl, aryl, hydroxy, alkoxy, cyano, carboxyl, sulfahydryl, alkylthio, amino, nitro, halo, carbonyl, carbamato, sulfamato, sulfanato, sulfato, and the like.

The term "amino acid" refers to molecules containing one or more amino and carboxyl groups. Examples of alfa-amino acids (D-, L- and DL- amino acids) -include natural alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. Other examples include beta-amino acids and known unnatural amino acids.

The term "amino acid ester" as used in this specification refers to an amino acid where the carboxyl group is substituted with a Ci-C ₈ alkyl group. That is, the alkyl group when taken together with the carboxyl group forms a Ci -C₆ alkyl ester. It is appreciated that some amino acids (e.g., aspartic acid and glutamic acid) have two carboxyl groups these may form mono- and di-esters.

The term "protecting group" (PG) refers to an 'amino protecting group' or a 'hydroxyl protecting group' or a 'carboxyl protecting group' and the like.

The term "amino protecting group" refers to a group that selectively blocks or protects the amino functionality in presence of other functional groups on the molecule. Examples of such amino-protecting groups include the formyl group, the trityl group, the

phthalimido group, the acetyl group, the trifluoroacetyl group, the chloroacetyl, bromoacetyl, and iodoacetyl groups, urethane-type blocking groups such as benzyloxycarbonyl ("CBZ"), 9-fluorenylmethoxycarbonyl ("FMOC"), tert-butoxycarbonyl ("BOC"), trichloroethylcarbonyl and the like. Additional examples of amino protecting groups are described by T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1991. Molecules with two or more amino groups may form mono-, di-, tri-, poly-, protected derivatives depending on the reaction conditions used.

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The term "hydroxyl protecting group" refers to a group that selectively blocks or protects hydroxyl functionality in presence of other reactive functional groups on the molecule. Examples of such hydroxyl-protecting groups include, for example, ether groups including methyl and substituted methyl ether groups such as methyl ether, methoxymethyl ether, methylthiomethyl ether, tert-buylthiomethyl ether, triphenylmethyl, tetrahydropuranyl (THP), (phenyldimethylsilyl)methoxy-methyl ether, benzyloxymethyl ether, p-methoxybenzyloxy-methyl ether, and tert-butoxymethyl ether; substituted ethyl ether groups such as ethoxyethyl ether, 1-(2-chloroethoxy)-ethyl ether, 2,2,2-trichloroethoxymethyl ether, and 2-(trimethylsilyl)ethyl ether; isopropyl ether groups; phenyl and substituted phenyl ether groups such as phenyl ether, p-chlorophenyl ether, p-methoxyphenyl ether, and 2,4-dinitrophenyl ether; benzyl and substituted benzyl ether groups such as benzyl ether, p-methoxybenzyl ether, o-nitrobenzyl ether, and 2,6dichlorobenzyl ether; and alkylsilyl ether groups such as trimethyl-, triethyl- and triisopropylsilyl ethers, mixed alkylsilyl ether groups such as dimethylisopropylsilyl ether, tert-butyldimethylsilyl ether and diethylisopropylsilyl ether; and ester protecting groups such as acetate ester, formate ester, benzylformate ester, mono-, di-, and trichloroacetate esters, pivalate ester, phenoxyacetate ester, and p-chlorophenoxyacetate, 9-fluorenylmethoxycarbonate, tert-butoxycarbonate, benzyloxycarbonate, trichloroethylcarbonate, carbamate, sulfamate and the like. Additional examples of hydroxyl protecting groups are described by T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1991. Molecules with two or more hydroxyl groups may form mono- and di-esters/ethers depending on the reaction condition.

The term "carboxyl protecting group" refers to a group that selectively blocks or protects carboxyl functionality in presence of other reactive functional groups on the molecule. Examples of such carboxyl-protecting groups include, for example (substituted) alkyl esters such methyl ester, ethyl ester, t-butyl ester, (substituted) benzyl ester, trichloroethyl ester, and the like. Additional examples of carboxylic acid protecting groups are described T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1991. Molecules with two or more carboxylic acid groups may form mono-, di-, tri-, tetra-, poly- protected derivatives depending upon the reaction conditions used.

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The term "carbonyl activating group" refers to leaving group ("LG") of a carboxyl derivative that is easily replaced by an incoming nucleophile. Such "LG" groups include, but are not limited to, (substituted) alkoxy, aryloxy, nitrogen containing unsaturated heterocycles such as N-oxybenzotriazole, imidazolyl, o/p-nitrophenoxy, pentachlorophenoxy, N-oxysuccinimide, N,N'-dicyclohexylisoure-O-yl, N-hydroxy-N-methoxyamino, and the like; acetates, formates, sulfonates such as methanesulfonate, ethanesulfonate, benzenesulfonate, or p-toluenesulfonate, and the like; and halides especially fluoride, chloride, bromide, or iodide.

The term "carbonyl activating reagent" refers to a reagent that converts the carbonyl of a carboxylic acid group into one that is more susceptible to nucleophilic attack and includes, but is not limited to, such reagents as those found in "The Peptides", Gross and Meienhofer, Eds., Academic Press (1979), Ch. 2, and M. Bodanszky, "Principles of Peptide Synthesis", 2.sup.nd Ed., Springer-Verlag Berlin Heidelberg, 1993, hereafter referred to as "The Peptides" and "Peptide Synthesis" respectively. Carbonyl group (i.e., aldehyde or keto group) of candidate drugs may be converted first to aldoxime, ketoxime, hydrazone, semicarbazone and the like, before coupling to the linker. Specifically, carbonyl activating reagents include thionyl bromide, thionyl chloride, oxalyl chloride, and the like; esters of alcohols such as nitrophenol, pentachlorophenol, and the like; and compounds such as l,l'-carbonyldiimidazole (CDI), benzotriazole, imidazole, N-hydroxysuccinimide, dicyclohexylcarbodiimide (DCC), EDC, phosgene or its equivalents, N, N-dimethylaminopyridine (DMAP) and the like.

The terms "phosgene or its equivalents" refer to phosgene or it equivalents such as diphosgene, triphosgene, CDI, DSC, BTBC, alkoxycarbonyl chlorides, o/p-nitrosubstituted phenoxycarbonyl chlorides, and the like.

In general, the term "pharmaceutical" when used as an adjective means substantially non-toxic to living organisms.

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The terms "pharmaceutically acceptable metal ions or salts" refer to salts of the compounds of this invention, which are substantially non-toxic to living organisms. See, e.g., Berge, S. M. et al., "Pharmaceutical Salts", J. Pharm. Sci., 66:1, 1977. Typical pharmaceutical salts include those salts prepared by reaction of the compounds of this invention with an inorganic or organic acid or base. Such salts are known as acid addition or base addition salts respectively. These pharmaceutical salts frequently have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions. Examples of pharmaceutically acceptable salts are those with inorganic bases such as sodium, potassium, calcium, magnesium, and hydroxides, and the like, or with organic bases such as lysine, arginine, triethylamine, dibenzylamine, piperidine, and the like.

The term "suitable solvent" refers to a solvent that is inert to the ongoing reaction and sufficiently solubilizes the reactants to effect the desired reaction. Examples of suitable solvents include but are not limited to, dichloromethane, chloroform, 1,2-dichloroethane, diethyl ether, tert-butylmethyl ether, acetonitrile, ethyl acetate, 1,3-dimethyl-2-imidazolidinone, tetrahydrofuran, dimethylformamide, benzene, toluene, xylene, N-dimethylacetamide, N-methylpyrrolidine, chlorobenzene, dimethylsulfoxide, dimethoxyethane, water, methanol, ethanol, isopropanol, pyridine, nitromethane, mixtures thereof, and the like.

The term "suitable base" refers to a base, which acts as a proton trap for any protons, which may be produced as a byproduct of the desired reaction, or to a base, which provides a reversible deprotonation of an acidic proton from the substrate and is reactive enough to effect the desired reaction without significantly effecting any undesired reactions. Examples of such bases include, but are not limited to, carbonates, bicarbonates, and hydroxides (e.g., lithium, sodium, potassium, magnesium, calcium and the like), sodium/potassium/calcium hydride, sodium/potassium alkoxide (i.e.,

methoxide, ethoxide, tert-butoxide and the like), triethylamine, diisopropylethylamine, N-methylpyrrolidine, N-methylmorpholine, tetramethylguinidine, or aromatic nitrogen containing heterocycles such pyridine, 4-(dimethylamino)pyridine (DMAP), and the like.

The term "NONOate" refers to a linkable nitric oxide-releasing group such as AcOCH₂-O-N₂-N(OOR⁷, OCHOCH₂-O-N₂-N(O⁻) R⁷R⁷, CH₂-O-N₂-N(OOR⁷ R⁷ and the like.

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The term "therapeutic agent" refers to biologically active molecules such as drugs, vitamins, and other molecules, agents or substances concerned with or contributing to the treatment and cure of illness or contributing to the general well being of a mammal or human. The therapeutic agents can be both known and investigational drugs compiled in drug databases such as the Merck Index, IDdb, Prous Science's Integrity®, Prous Science Drugs of the FutureTM, The Ensemble® and the like. The Merck Index is a one-volume encyclopedia of chemicals, drugs and biologicals that contains more than 10,000 monographs. Each monograph in this authoritative reference source is a concise description of a single substance or a small group of closely related compounds. Prous Science is an international health science publishing company, established in 1958 and headquartered in Barcelona, Spain. Prous Science Drugs of the FutureTM, produced by Prous Science Publishers, contains comprehensive drug monographs providing product information on new compounds, including the synthesis and corresponding schemes, pharmacological action, pharmacokinetics and metabolism, toxicity, clinical studies, manufacturer, and references. Information on compounds is continuously updated as advances in development status are disclosed worldwide. The Prous Science Integrity™ is a drug R&D portal where knowledge areas are coordinated to provide a harmonious and interrelated whole, which includes Drugs & Biologies, Targets, Organic Synthesis, Experimental Pharmacology, Pharmacokinetics and Metabolism, Clinical Studies, Disease Briefings, Companies & Markets, Literature and Patents. The Investigational Drugs database (IDdb), developed by Thomson Current Drugs, is a pharmaceutical competitor intelligence service. It covers all aspects of investigational drug development, from first patent to eventual launch or discontinuation. The Ensemble® on the Web provides essential information, including chemical structures, on more than 140,000

compounds with demonstrated biological activity in the drag research and development pipeline.

The term "vitamin" includes vitamin A, vitamin C, thiamine, folic acid, biotin, inositol, nicotinic acid, nicotinamide, riboflavin, pyridoxine, pyridoxal 5-phosphate, ergosterol, vitamin D2, vitamin D3, vitamin D4, vitamin E, menadoxime, menadiol, and vitamin K5.

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The term "peptide" includes large and small peptides, including, but not limited to, targetable small peptides such as a dipeptide, tripeptide, tetrapeptide, etc.

The term "ligand" means a small molecule that binds to a larger macromolecule, whether or not the ligand actually binds at a metal site. Such ligands can be small peptides.

One aspect of the invention is to provide mutual prodrugs of two or three therapeutic agents currently used for use in combination therapy utilizing novel biocleavable linkers, water-soluble prodrugs of insoluble and sparingly-soluble therapeutic agents using the same linker technology, and water-soluble double and triple prodrugs of sparingly-soluble therapeutic agents using the same linker technology. The embodiments of the invention may also comprise vitamins and targetable small peptides in addition to or in place of a promoeity to yield targetable prodrugs.

The candidate drugs selected for mutual prodrug synthesis can be from one therapeutic category or from different therapeutic categories. Similarly, the constituent drugs of a mutual prodrug can act on the same biological target with similar mechanism of action or act on different biological targets with different mechanisms of action.

To be considered for prodrug synthesis, the candidate drugs should contain one or more of the essential functional groups such as amino, hydroxyl, keto, or carboxyl groups in their structure.

Amino group of the candidate drug can be primary or secondary (both acyclic and cyclic) which include amide-NH, sulfonamide-NH, carbamate-NH, sulfamate-NH, hydrazone-NH, semicarbazone-NH, thiosemicarbazone-NH and also drags containing indole, imidazole, benzimidazole, thiazole, oxozole, pyrrole, pyrazole, triazole, tetrazole, or similar NH-containing heterocylic sub-structures of a more complex drag molecule. Similarly, hydroxyl group of drags can be of primary, secondary or tertiary nature. Keto

group of candidate drugs may be converted first to ketoxime, hydrazone, semicarbazone and then like, before coupling to the linker. Obviously, hydroxyl or amino functions thus generated will be used to form covalent bond between the drug and the linker.

The candidates for making mutual prodrugs can be the pairs of drugs that are currently used in combination therapy (including those combination studies at investigational stage) in various therapeutic areas provided each of those drugs possesses the requisite functional group(s). There are a number of therapeutic areas where such combination therapy is applied routinely and successfully.

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On the basis of the proposed sulfahydryl-dependent mechanism of NO-release from GTN, we have designed the compounds and prodrugs of the present invention where a suitable drug molecule is linked covalently to a nitrooxy (nitrate ester) group via a bio-labile linker containing strategically located disulfide bond at Z?efø-position to nitrate ester. In vivo, the disulfide bond in the prodrug is expected to be reduced by endogenous sulfahydryl-containing species such as glutathione (GSH) to generate a reactive thiolate anion (i.e., beto-mercapto-nitrate), which can trigger further break-down of the linker moiety to release the free drug (via a mechanism as shown Scheme Ml) and NO simultaneously at the same location. It is possible, as depicted in the mechanism Scheme Ml, the release of NO can go via a hypothetical cyclic transient intermediate 'b'. Similar hypothetical mechanism was proposed for NO release from SS-nitrates, which were also designed on the basis of a sulfahydryl-dependent NO release from GTN. See, for example, Zavorin, S. I. et al., Organic Letters, 2001, 3, 1113, incorporated herein in its entirety. Mutual prodrugs can be made by linking covalently any two of the following: an amino-containing therapeutic agent to another ammo-containing therapeutic agent; an amino-containing therapeutic agent to a hydroxyl-containing therapeutic agent; an aminocontaining therapeutic agent to a carboxyl-containing therapeutic agent and its derivative; a hydroxyl-containing therapeutic agent to a carboxyl-containing therapeutic agent and its derivative; an amino-containing therapeutic agent to a carboxyl-containing therapeutic agent and its derivative; an amino-containing therapeutic agent to a keto-containing therapeutic agent or its hydazone, semicarbazone or oxime derivative and the likes; a hydroxyl-containing therapeutic agent to a keto-containing therapeutic agent via its hydrazone, semicarbazone, or oxime derivative and the likes.

Another aspect of the present invention is to provide new nitrate ester (NO-releasing) prodrugs of many types of existing drugs using novel biocleavable likers. Such prodrugs are expected to exhibit better efficacy and tolerability with reduced side effects compared to the corresponding original drugs.

An embodiment of present invention relates to the compounds of formula (I) or pharmaceutically acceptable salts thereof:

$$D^{1} \stackrel{L^{1}}{=} A \stackrel{A}{=} A^{1} \stackrel{L}{=} \left(\stackrel{L}{=} A^{1} \stackrel{A}{=} A \stackrel{L^{2}}{=} D^{2} \right)$$
Formula (I)

10 wherein,

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a is 0-2;

B independently represents a bond, $(CH_2)_b$, $(CH_2CH_2O)_c$, S-S, S-S=O, S-SO₂ or S-S=NH; b is 1-6; c is 1-1000;

A and A¹ independently represent a bond, (CH₂)d, 1,2-phenylene, 1,3-phenylene or 1,4-phenylene;

d is 1-8;

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D¹ represents a therapeutic agent comprising one or more of the functional groups selected from the group consisting of -OH, -SH, -NHR¹, -CO₂H, -CONHR¹, -OC(=O)NHR¹, -SO₂NHR¹, -OSO₂NHR¹, -N(R¹)C(=O)NHR¹ and -N(R^SO₂NHR¹;

D² independently represents D¹, a peptide, protein, monoclonal antibody, vitamin, R², R³, R⁴, NO, NO₂, a linkable nitric oxide-releasing group comprising a NONOate, a group comprising one or more of water-solubilizing functional groups, or a polymer; E independently represents CH₂ or a bond;

L¹ and L² independently represent a bond, O, S, NR¹, L, or a linkage selected from the

25 group consisting of:

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$$X \rightarrow X$$
, $X \rightarrow X$, X

L is R¹² or a group with bonding in any direction, independently selected from the group consisting of:

X independently represents a bond, C, O, S, or NR1;

Y independently represents a bond, C=O, C=S, S=O, SO₂, P(=0)XR\ or (CH₂)_d;

Z independently represents a bond, or (CH₂)J; wherein, j is 1-4;

10 R¹ independently represents a bond, H, (Ci-C₈)alkyl, (C₅-Ci₄)aryl, aralkyl or M⁶⁺;

R² independently represents H, NH₂, or NHAc;

R³ independently represents H, CO₂R⁵, CH₂CO₂R⁵,

R⁴ independently represents H, OH, O-(Ci-Cs)alkyl, OM^{e+}, or a group selected from the group consisting of:

$$CO_2R^6$$
, $CH_2CO_2R^6$, $CH_2CO_2R^6$, CO_2R^6 , C

M independently represents Na, K or a pharmaceutically acceptable metal ion,

e = 1-3,

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 R^5 independently represents at each occurrence H, $M^{6+},$ (C_1-C_8) alkyl, (C_3-C_8) cycloalkyl, substituted (C_5-Ci_4) aryl, hetero(C_2-C_{14}) aryl, $C(=O)(CH_2)_fCHR^9CO_2R^5,$ $CH_2C(=O)OR^5,$ $P(=O)(OR^5)_2$,

$$CO_2R^6$$
, $CH_2CO_2R^6$, $CH_2CO_2R^6$, $CH_2-Dextran$, CO_2R^6

 X^2 independently represents O, S, SO, SO_2 , or NR^5 ;

 R^6 independently represents H,Na^+,K^+ , any other pharmaceutically acceptable metal ion,

(Ci-C₈)alkyl, or (C₃-C₈)cycloalkyl,

R⁷ independently represents at each occurrence same or different R⁵;

5 R⁸ independently represents CH₂, O, NR⁴, S, S=O or O=S=O;

R⁹ independently represents H, (Ci-C₈)alkyl or an amino acid;

f is 0-6;

g is 0-1;

h is 1-2000;

10 i is 1-4;

 R^{10} and R^{11} independently represent H, (Ci-C₈)alkyl, (C₃-C₈)cycloalkyl, or a group selected from the group consisting of:

with a proviso that when R^{10} is selected from the above group, R^{11} represents H or (Ci-C₈)alkyl, and when R^{11} is selected from the above group, R^{10} represents H or (Q-C₈)alkyl;

5 R¹² independently represents a group selected from the group consisting of:

5 X^3 is independently O or NR⁷.

D¹ and D² of the present invention can be both known and investigational drugs compiled in drug databases such as the Merck Index, IDdb, Prous Science's Integrity[®],

Prous Science Drugs of the FutureTM, The Ensemble[®] and the like. In a double prodrug, D¹ and D² are the same drugs. In a mutual prodrug, D¹ and D² are different drugs. In some prodrugs, only D¹ is a drug and D² may not be a drug at all. The -OH, -SH, -NH₂, -NHR¹, -CO₂H, -CONHR¹, -OCC=O)NHR¹, -SO₂NHR¹, -OSO₂NHR¹, -N(R^CC=O)NHR¹ and -N(R^SO ₂NHR¹ functional groups in D¹ and D² of formula I participate in the formation of linkages between the drug and the linker. Accordingly, some of the atoms or groups in L¹ and L² may come from the corresponding D¹, D² or linker.

Another embodiment of the invention is the compound of formula I, wherein D² is an amino-, carboxyl- or hydroxyl- containing group or molecule comprising one or more water solubilizing functional groups selected from the group consisting of hydroxyl, amino, acylamino, carboxyl, sulphate, sulfonate, phosphate, phosphonate, N-acylsulfonamide, N-acylsulfamate, N-acylcarbamate, N-acylcarbamate metallic salts, and amino acids to give water-soluble prodrug.

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Another embodiment of the invention is the compound of formula I, wherein D^2 is selected from the group of D, L and DL amino acids consisting of Alanine, Arginine, Asparagine, Aspartic acid, Cysteine, Glutamine, Glutamic acid, Glycine, Histidine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Proline, Scrine, Threonine, Tryptophan, Tyrosine, and Valine.

Another embodiment of the invention is the compound of formula I, wherein D² represents a polymer selected from the group consisting of arabinogalactan, polyamino acids, polyethylene glycol, polycaprolactone, polyglycolic acid, polylactic acid, polyacrylic acid, poly(2-hydroxyethyl 1-glutamine), dextran and modified dextrans such as dextran aldehyde, carboxymethyl dextran, arabinogalactane aldehyde, carboxymethyl arabinogalactane, and hyaluronic acid.

Yet another embodiment of the invention is the compound of formula I, wherein D² is a polyaminoacid selected from group consisting of poly(l-glutamic acid), poly(d-glutamic acid), poly(d-glutamic acid), poly(d-aspartic acid), poly(dl-aspartic acid), poly(dl-aspartic acid), poly(dl-aspartic acid), copolymers of the polyaminoacids and polyethylene glycol,

Another embodiment of the invention is the compound of formula I, wherein the polymer has a molecular weight of about 5000 to about 100,000 Daltons. Yet another

embodiment of the invention is the compound of formula I, wherein the polymer has a molecular weight of about 10,000 to about 50,000 Daltons.

In a further embodiment D^2 is a peptide, protein or monoclonal antibody for achieving targeted delivery of prodrugs and drugs. Another embodiment of the invention is the compound of formula I, wherein D^2 is a ligand or dipeptide or a dipeptide ligand. In a further embodiment D^2 is a dipeptide ligand that is a substrate for intestinal transporters for selective intestinal absorption of the corresponding prodrugs thereby increasing the bioavailability of the prodrugs. In a further embodiment D^2 is a targetable small peptide, i.e., dipeptide, tripeptide, tetrapeptide, etc.

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Another embodiment of the invention is the compound of formula I, wherein D² is a vitamin. Such vitamin-conjugated prodrugs are expected to be taken up by the diseased cells via receptor-mediated endocytosis. In a further embodiment of the invention is a compound of formula I, wherein D² is selected from the group of vitamins consisting of vitamin A, vitamin C, thiamine, folic acid, biotin, inositol, nicotinic acid, nicotinamide, riboflavin, pyridoxine, pyridoxal 5-phosphate, ergosterol, vitamin D2, vitamin D3, vitamin D4, vitamin E, menadoxime, menadiol, and vitamin K5.

Another embodiment of the invention is the compound of formula I, wherein D¹ and D² represent the same therapeutic agent to give a symmetrical double prodrug. Another embodiment of the invention is the compound of formula I, wherein D¹ and D² represent different therapeutic agents to give a mutual prodrug. Another embodiment of the invention is the compound of formula (I), wherein D¹ and D² can be either from same or different therapeutic class. Another embodiment of the invention is the compound of formula (I), wherein D¹ and D² can be same or different therapeutic agents. Such therapeutic agents may have same or different mechanisms of action or they may work on different biological targets or work on different disease conditions.

Another embodiment of the invention is the compound of formula I, wherein D^2 is R^2 , R^3 or R^4 . Another embodiment of the invention is the compound of formula I, wherein a is 0, B is S-S, S-S=O, S-SO₂ or S-S=NH. Yet another embodiment of the invention is the compound of formula I, wherein a is 0, B is S-S or S-S=O, S-SO₂ and D^2 is R^2 or R^3 or R^4 . A further embodiment of the invention is the compound of formula I, wherein B is S-S, A and A^1 are CH_2 - CH_2 , E is a bond and D^2 is R^2 , R^3 or R^4 .

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Another embodiment of the invention is the compound of formula I, wherein a is 0; B is S-S or S-S=O, S-SO₂; A and A¹ are CH_2 -CH, E is a bond and D² is R⁴. Another embodiment of the invention is the compound of formula I, wherein a is 0; B is S-S; A and A¹ are CH_2 -CH₂, E is a bond and D² is R⁴.

Another embodiment of the invention is the compound of formula I, wherein a is 0, B is a bond, $(CH_2)b$, or $(CH_2CH_2O)_0$; wherein b and c are as defined above. Another embodiment of the invention is the compound of formula I, wherein a is 0, B is a bond, $(CH_2)_b$ or $(CH_2CH_2O)_0$ and D^2 is R^2 or R^3 or R^4 ; wherein b and c are as defined above.

Yet another embodiment of the invention is the compound of formula I, wherein a is 0; B is S-S or S-S=O, S-SO₂; D¹ and D² are drug molecule or R² or R⁴ containing carboxyl group; L¹ and L² are independently selected from the following linkages:

wherein, X, R^1 , Z are as defined above; and Y is C=O. In another embodiment, A and A^1 are CH_2 - CH_2 , and E is a bond. In a further embodiment, A and A^1 are 1, 2-phenylene, 1, 3-phenylene or 1, 4-phenylene, and E is CH_2 .

Yet another embodiment of the invention is the compound of formula I, wherein a is 0; B is S-S or S-S=O, S-SO₂; D¹ and D² are drug molecule or R² or R⁴ containing amino- or hydroxyl group; L¹ and L² are independently selected from the following linkages:

wherein, X, R^1 , Z are as defined; and Y is C=O. In another embodiment, A and A^1 are CH_2 - CH_2 , and E is a bond. In a further embodiment, A and A^1 are 1, 2-phenylene, 1, 3-phenylene or 1, 4-phenylene, and E is CH_2 .

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Yet another embodiment of the invention is the compound of formula I, wherein a is 0, B is S-S or S-S=O, S-SO₂ and D² is D¹. Another embodiment of the invention is the compound of formula I, wherein a is 0; B is S-S or S-S=O, S-SO₂; A and A¹ are CH₂-CH₂, E is a bond and D² is D¹. Another embodiment of the invention is the compound of formula I, wherein a is 0; B is S-S or S-S=O, S-SO₂; A and A¹ are 1,2-phenylene, 1,3-phenylene or 1,4-phenylene; E is CH₂ and D² is D¹Or R² or R³ or R⁴. Another embodiment of the invention is the compound of formula I, wherein a is 0; B is S-S; A and A¹ are 1,2-phenylene, 1,3-phenylene or 1,4-phenylene; E is CH₂ and D² is D¹Or R² or R³ or R⁴. A further embodiment of the invention is the compound of formula I, wherein B is S-S, A and A¹ are CH₂-CH₂, E is a bond and D² is D¹.

Yet another embodiment of the invention is the compound of formula I, wherein a is 0; B is S-S or S-S=O, S-SO₂; A and A¹ are CH_2 - CH_2 , E is a bond and D² is a dipeptide ligand. Yet another embodiment of the invention is the compound of formula I, wherein a is 0; B is S-S; A and A¹ are CH_2 - CH_2 , E is a bond and D² is a dipeptide ligand. The peptide ligands used in the invention can be substrates for intestinal transporters for selective intestinal absorption of the corresponding prodrugs thereby increasing the bioavailability of the prodrugs. An embodiment of the present invention is the compounds of formula (I), wherein D¹, L¹ and L² are as defined above; A and A¹ are CH_2 ; E is CH_2 ; B is a bond or $(CH_2)_b$; b is 1-6; a is 0; and D² is D¹ or R² or R⁴.

Another embodiment of the present invention is the compound of formula (I), wherein E, D¹ and L¹ are as defined; L² is O; A and A¹ are independently $(CH_2)_d$, 1,2-phenylene, 1,3-phenylene, or 1,4-phenylene; d is 1-4; B is S-S, S-S=O, S-SO₂ or S-S=NH; a is 0; D² is NO, NO₂ or a nitric oxide releasing molecule such as NONOate. In a further embodiment, D² is a NONOate selected from the group consisting of:

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Another embodiment of the present invention is the compound of formula (I), L^2 is O; A and A^1 are independently $(CH_2)a$, 1,2-phenylene, 1,3-phenylene, or 1,4-phenylene; d is 1-4; B is S-S; a is 0; D^2 is NO_2 . In a further embodiment, when A and A^1 CH_2 - CH_2 , E is a bond. In yet another embodiment, when E is CH_2 , A and A^1 are independently 1,2-phenylene, 1,3-phenylene, or 1,4-phenylene.

Yet another embodiment of the present invention is the compound of formula (I), wherein D¹ is a amino containing drug molecule having the following reactive functional groups which are involved in the formation of L¹ linkages between the drug and the linker: -NH₂,-NHR¹, -CONHR¹, -0-C(K))NHR¹, -SO₂NHR¹, -OSO₂NHR¹, -NR¹Q=O)NHR¹ or -N(R^SO₂NHR¹; L² is O; E is bond; L¹ is linkages selected from the group consisting of:

wherein, X is independently a bond, O or NR¹, Y is C=O or SO₂, A and A¹ are CH₂ CH₂, B is S-S, a is Oand D² is NO₂.

An embodiment of the present invention is the compound of formula (I), wherein D^{1} is a hydroxyl or sulfahydryl containing drug molecule such as Drug-OH or Drug-SH, wherein functional groups OH and SH are involved in the formation of L^{1} linkages between the drug and the linker; L^{2} is O; E is bond, L^{1} is a linkage selected from the group consisting of:

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wherein, X is independently a bond, O or NR¹, R1 is not a bond, Y is C=O or SO₂, A and A¹ are CH₂CH₂; B is S-S; a is 0; and D² is NO₂.

An embodiment of the present invention is the compound of formula (I), wherein D¹ is a drug molecule having carboxyl (-CO₂H) as a reactive functional group such as -CO₂H which is involved in the formation of L¹ linkages between the drug and the linker; L² is O; E is bond; L¹ is O or NR¹ or a linkage selected from the group consisting of:

wherein, X is independently a bond, O or NR¹, R¹ is not a bond; Y is C=O or SO₂; A and A¹ are CH₂CH₂; B is S-S; a is O and D² is NO₂.

Another embodiment of the present invention is the compounds of formula (I), wherein D¹ is an antioxidant or free radical scavenger such as a hydroxyl-containing stable radical such a 4-hydroxy-2,2,6,6-tetramethylpiperidin-l-oxyl (4-hydroxy-TEMPO), 4-carboxy-2,2,6,6-tetramethylpiperidin-l-oxyl (4-carboxy-TEMPO) or any other ammo-/carboxyl-/hydroxyl-containing antioxidants or radical/super oxide scavengers, and D² is NO₂. The amino-/carboxyl-/hydroxyl-containing antioxidants and radical/super oxide scavengers can be known or investigational.

An embodiment of the present invention is the compound of formula (I), wherein

L¹ is
$$\stackrel{\times}{\times}$$
 X or $\stackrel{\times}{\mathbb{R}^1}$; wherein, X is a bond, O, S or NR¹; L² is O, E is a bond; A and A¹ are CH₂CH₂; B is S-S; a is o; and D² is NO₂.

An embodiment of the present invention is the compounds of formula (I), wherein $D^{!}$ and L^{1} are as defined above; L^{2} is O; A is 1,2-phenylene, 1,3-phenylene, or 1,4-phenylene; A^{1} is CH_{2} ; E is CH_{2} ; B is S-S; a is 0 and D^{2} is NO_{2} .

An embodiment of the present invention is the compounds of formula (I), wherein L^2 is O; A and A¹ are CH_2 ; E is CH_2 ; B is a bond or $(CH_2)_b$; b is 1-6; a is O; D^2 is NO_2 and L^1 is a group selected from

wherein, X is O, S or NR1; R1 is as defined.

An embodiment of the invention is the compound of formula I selected from the groups consisting of:

A. Prodrugs:

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(a) From carboxyl-containing drugs:

(b) From amino-containing drugs:

$$\begin{array}{c} H_3C \\ \\ H_3C \\ \\ H_3C \\ \\ H_3C \\ \\ \end{array}$$

 R_{y1} = An amino-, hydroxyl-containing molecule with water-solubilizing groups I-A2-PD5

s = 1, 2; R^{a1} = H, OH, NH2, or a substituted amino group I-A3-PD6

R^{a2} = Me or any alkyl, aryl, aralkyl, or another sulfonamide containing drug such as valdecoxib, celecoxib, and the like.

I-A3-PD7b

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(c) From hydroxyl-containing drugs:

$$\begin{array}{c} NO_2 \\ NO_2 \\ NO_3 \\ CH_3 \\ I-H1-PD1 \\ NO_2 \\ CH_3 \\ I-H1-PD2 \\ CH_3 \\ I-H1-PD3 \\ CH_3 \\ I-H1-PD3 \\ CH_3 \\ I-H1-PD3 \\ CH_3 \\ R = H, \text{ lower alkyl, etc.} \end{array}$$

$$X^{1} = H, X^{2} = 0$$

$$X^{1} = H, X^{2} = 0$$

$$I-Taxol-PD1: R^{x22} = H$$

$$I-Taxol-PD2: R^{x22} = C(=0)CH_{2}CH_{2}CO_{2}H$$

$$CH_{3} \qquad CH_{3} \qquad CH_{$$

A PRODRUG OF ISOTAXEL I-S23-PD1

Y = O, NR | (R | = H, Alkyl, Aralkyl, Cycloalkyl), (CH₂)_nC(=O) (n=l-6), (CH₂)_nCO₂-Z = C=O, SO₂, P(=O)YR ³ (R³ = H or a metal ion)

 $R^2 = H$, a bond, $CH_2CH_2N(CH_3)_2$. HCl, an Amino acid, or any molecule containing solubilizing groups such as carboxylic acid, sulphonic acid, hydroxyl, amino groups, polyethyleneglycol (PEG), a metal ion such a Na⁺, Ca ²⁺, etc.

- B. NO-releasing Prodrugs
 - (a) From carboxyl-containing drugs

(b) From amino-containing drugs

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$$H_3C$$
 $N_{3}C$
 $N_{$

(c) From hydroxyl-containing drugs

- 5 C. Mutual or Double Prudrugs
 - (a) From two amino-containing drugs

$$\begin{split} R^{aa1} &= H, \, PO_3H_2, \, C(O)NHCH_2CH_2NMe_2, \, C(O)CH2NR'2 \, (R'=H \, or \, Alkyl), \\ C(O)OCH_2CH_2NMe_2, \, C(O)CH_2CH_2CO_2H, \, C(O)NHCH_2CH_2NHCOCH_2CH_2CO_2H, \\ C(O)O(CH_2)_2NHCO(CH_2)_2CO_2H, \, and \, C(O)CH_2N(CH_2CO_2H)_2. \end{split}$$

I-AA-MPD3a (Raal= H)

(b) From two carboxyl-containing drugs

(c) From two hydroxyl-containing drugs

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(d) From an amino-containing drug and a carboxyl-containing drug:

(e) Mutual prodrugs of one carboxyl-containing and one hydroxyl-containing drugs

(f) Mutual prodrugs of one amino-containing and one hydroxyl-containing drugs

An embodiment of the invention is a pharmaceutical composition comprising a therapeutically effective amount of the compound of formula I, or a pharmaceutical salt thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.

Another embodiment of the invention is a pharmaceutical composition 5 comprising a therapeutically effective amount of the compound of formula I selected from the group consisting of I-C1-PD1, 1-C1-PD2, 1-C1-PD3, 1-C1-PD4, 1-C1-PD4a, I-C1-PD4 CI-PD4b, I-C1-PD5, 1-C1-PD6, 1-C1-PD7, 1-C1-PD8, 1-C1-PD9, 1-C1-PD10, I-C1-PD10, I-C1-PD PDII, I-C1-PD12, 1-C1-PD13, 1-C1-PD14, 1-Cl-PD15a, I-Cl-PD15b, I-A1-PD1, I-Al-PD2, 1-A1-PD3, 1-A1-PD4, 1-A1-PD5, 1-A1-PD6, 1-A1-PD7, 1-A1-PD8, 1-A1-PD9, I-A1-PD9, I 10 PDIO, I-A1-PD11, 1-A1-PD12, 1-A1-PD13, 1-A1-PD14, 1-A1-PD15A, I-A1-PD15Aa, I-A1-PD15AAA, I-A1-PD15AA, I-A1-PD A1-PD15B, I-A1-PD15Bb, I-A1-PD16, 1-A1-PD17, 1-A2-PD1, 1-A2-PD2, 1-A2-PD2b, I-A2-PD3a, I-A2-PD3b, I-A2-PD4, 1-A2-PD5, 1-A3-PD1, 1-A3-PD2a, I-A3-PD2b, I-A3-PD3a, I-A3-PD3b, I-A3-PD4, 1-A3-PD5, 1-A3-PD6, 1-A3-PD7b, I-H1-PD1, 1-H1-PD2, I-H1-PD3, 1- H1-PD4, 1- H1-PD5, 1- H1-PD6, 1- H1-PD7, 1- H1-PD8, 1- H1-PD9, 1- H1-PD9 PDIO, I- HI-PDII, I- H1-PD12, I- H1-PD13, I-Taxol-PD1, I-Taxol-PD2, I-Taxol-PD3, 15 I-Taxol-PD4, 1-Taxol-PD5, 1-Taxol-PD6, 1-S23-PD1, 1-C1-NOPD1, 1-C1-NOPD2, 1-Cl-NOPD3a, I-Cl-NOPD3b, I-Cl-NOPD4, 1-Cl-NOPD5a, I-Cl-NOPD5b, I-Cl-NOPD6, I-C1-NOPD7, 1-Cl-NOPD8a, I-Cl-NOPD8b, I-C1-NOPD9, 1-C1-NOPD10, 1-Cl-NOPDIIa, I-C1-NOPD13, 1-Cl-NOPD14a, I-Cl-NOPD14b, I-Cl-NOPD15b, I-Cl-NOPD 16, 1-C 1-NOPD 17a, I-C 1-NOPD 17b, I-C 1-NOPD 18, 1-C 1-NOPD 19, 1-Cl-20 NOPD20a, I-Cl-NOPD20b, I-Cl-NOPD21, 1-Cl-NOPD22, 1-Cl-NOPD23b, I-Cl-NOPD20b, I-Cl-NOPD NOPD24, 1-C1-NOPD25, 1-C1-NOPD26, 1-A1-NOPD1, 1-A1-NOPD2, 1-A1-NOPD3A, I-A1-NOPD3B, I-A1-NOPD4, 1-A1-NOPD5, 1-A1-NOPD6, 1-A1-NOPD7, 1-A1-NOPD8, 1-A1-NOPD9, 1-A1-NOPD10a, I-A1-NOPD10b, I-A2-NOPD1a, I-A2-NOPDIb, I-A2-NOPD2a, I-A2-NOPD2b, I-A3-NOPDIa, I-A3-NOPDIb, I-A3-25 NOPD2a, I-A3-NOPD2b, I-H1-NOPD1, 1-H1-NOPD2a, I-H1-NOPD2b, I-H1-NOPD3, I-H1-NOPD4, 1-H1-NOPD5b, I-H1-NOPD6, 1-H1-NOPD7, 1-H1-NOPD8, 1-H1-NOPD9, I-H1-NOPD10, 1-AA-MPD1, 1-AA-MPD2, 1-AA-MPD3a, I-AA-MPD4, 1-AA-MPD5, I-AA-MPD6, 1-AA-MPD7, 1-AA-MPD8, 1-AA-MPD9, 1-AA-MPD10, 1-AA-MPD1 1, I-AA-MPD12, 1-AA-MPD13, 1-AA-MPD14, 1-AA-MPD15, 1-AA-MPD16, 1-AA-MPD17, 30 I-AA-MPD18, 1-AA-MPD19, 1-AA-MPD20, 1-AA-MPD21, 1-AA-MPD22, 1-AA-

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MPD23, 1-AA-MPD24, 1-AA-MPD25, 1-AA-MPD26, 1-AA-MPD27, 1-CC-MPD1, 1-CC-MPD2, 1-CC-MPD3, 1-CC-MPD4, 1-CC-MPD5, 1-CC-MPD6, 1-HH-MPD1, 1-HH-MPD2, 1-HH-MPD3, 1-HH-MPD4, 1-HH-MPD5, 1-HH-MPD7, I-HH-MPD7, I-HH-MPD8, 1-HH-MPD9, 1-HH-MPD10, 1-HH-MPD11, 1-HH-MPD12, 1-HH-MPD13, 1-HH-MPD14, 1-HH-MPD15, 1-HH-MPD16, 1-HH-MPD17, 1-HH-MPD18, 1-HHAH-TMPD1, I-CA-MPD1, 1-CA-MPD2, 1-CA-MPD3, 1-CA-MPD4, 1-CA-MPD5, 1-CA-MPD6, MPD7, 1-CA-MPD8, 1-CA-MPD9, 1-CA-MPD10, 1-CA-MPD11, 1-CA-MPD12, 1-MPD13, 1-CA-MPD14, 1-CA-MPD15, 1-CA-MPD16, 1-CA-MPD17, 1-CA-MPD18, I-CA-MPD19, 1-CA-MPD20, 1-CA-MPD21, 1-CA-MPD22, 1-CA-MPD23, 1-CA-MPD24, 10 I-CA-MPD25, 1-CA-MPD26, 1-CA-MPD27, 1-CA-MPD28, 1-CA-MPD29, 1-CA-MPD30, 1-AH-MPD1, 1-AH-MPD2, 1-AH-MPD3, 1-AH-MPD4, 1-AH-MPD5, 1-AH-MPD6, 1-AH-MPD7, 1-AH-MPD8, 1-AH-MPD9, 1-AH-MPD10, 1-AH-MPD11, I-AH-MPD12, 1-AH-MPD13, 1-AH-MPD14, 1-AH-MPD15, 1-AH-MPD16, 1-AH-MPD17, I-AH-MPD 18, 1-AH-MPD19, 1-AH-MPD20, 1-AH-MPD21, 1-AH-MPD22, 1-AH-MPD23, I-AH-MPD24, 1-AH-MPD25, 1-AH-MPD26, 1-CH-MPD1, 1-CH-MPD2, 1-CH-MPD3, I-15 CH-MPD4, 1-CH-MPD5, and I-CH-MPD6 or a pharmaceutical salt thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.

An embodiment of the invention is a method of treating a mammal or human in need thereof comprising administering a therapeutically effective amount of the pharmaceutical composition comprising the compound of formula I.

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Another embodiment of the invention is the below listed novel intermediates:

2-((2-Hydroxyethyl)disulfanyl)ethyl acetate (LI-1a)

2-((2-(Trityloxy)ethyl)disulfanyl)ethanol (LI-1c)

2-((2-Hydroxyethyl)disulfanyl)ethyl nitrate (LI-2b)

2-((2-Hydroxyethyl)disulfanyl)-ethyl nitrate (LI-2c.TFA)

tert-Butyl 2-((2-bromoethyl)-disulfanyl)ethylcarbamate (LI-2e)

1,2-Bis(2-bromoethyl)disulfane (LI-3a)

2-((2-Aminoethyl)disulfanyl)ethyl nitrate.acid salt (LI-5.TFA)

2-((2-(Tetrahydro-2*H*-pyran-2-yloxy)ethyl)disulfanyl)ethanol (**LI-1b**)

2-((2-Hydroxyethyl)disulfanyl)ethyl 2-chloroacetate (**LI-1d**)

2-((2-Bromoethyl)disulfanyl)ethanol (LI-2a)

tert-Butyl 2-((2-hydroxyethyl)disulfanyl)ethylcarbamate (LI-2c)

2-((2-(tert-Butoxycarbonylamino)ethyl)-disulfanyl)ethyl methanesulfonate (LI-2d)

tert-Butyl 2-((2-(nitrooxy)ethyl)-disulfanyl)ethylcarbamate (LI-2f)

$$O_2N_O$$
 S_S
 O_{NO_2}

2,2'-Disulfanediylbis(ethane-2,1-diyl) dinitrate (LI-3b)

$$H_2N$$
 $S \setminus_S$ $O \setminus_{NO_2}$

2-((2-Aminoethyl)disulfanyl)ethyl nitrate (LI-5)

2-((2-Bromoethyl)disulfanyl)ethyl carbonochloridate (**LI-6**)

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Another embodiment of the invention is use of the above listed novel intermediates in the processes for the preparation of compounds of formula I;

2-((2-((2,5-Dioxopyrrolidin-l-yloxy)carbonyloxy)ethyl)-disulfanyl)ethyl 2-(dimethylamino)ethylcarbamate (LI-10)

Further embodiments include methods of preparation and methods of use of compounds of formula (I) or pharmaceutically acceptable salts thereof.

Another embodiment of the invention is process for the preparation of compounds of formula I, or pharmaceutically acceptable salts thereof, wherein the process comprises of:

monoprotection of Bis-(2-hydroxyethyl)disulphide (SL-I) with an appropriate hydroxyl protecting group to give a corresponding monoprotected intermediate,

conversion of the corresponding monoprotected intermediate to an activated formyl intermediate by treating with phosgene or its equivalent, and

reaction of the activated formyl intermediate with an appropriate amino- or hydroxy containing D^1 to give the corresponding compound of formula I.

Another embodiment of the invention is a process for the preparation of compounds of formula I, or pharmaceutically acceptable salts thereof, wherein the process comprises of:

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-converting carboxy containing D1 into an activated intermediate comprising acyl halide, imidazolide or isocyanate, and

-reacting the activated intermediate with a linker intermediate to obtain the compound of formula I.

In another embodiment, the invention is a process in which the monoprotected intermediate is LIIx, and the activated formyl intermediate is Lllxy.

Another embodiment of the invention is a process for preparation of compounds of formula (I), wherein D_2 is NO_2 or pharmaceutically acceptable salts thereof, wherein the process comprises, mixing a selectively protected and activated D1 with a solution of 2-((2-hydroxyethyl)dithio)ethyl nitrate (LI-2b) in a suitable solvent in presence of a suitable coupling agent.

Another embodiment of the invention is a process for preparation of compounds of formula (I), wherein D² is NO₂ or pharmaceutically acceptable salts thereof, wherein a process comprises, converting 2-((2-hydroxyethyl)dithio)ethyl nitrate (LI-2b) into its formyl halide or imidazolide (LI-4x) by using a phosgene or its equivalent reagent and mixing/reacting the resulting reactive intermediate with a suitable amino- or hydroxycontaining drug in suitable solvent in presence of a suitable base.

Another embodiment of the invention is a process for preparation of compounds of formula (I), wherein D² is NO₂ or pharmaceutically acceptable salt thereof, wherein the process comprises, mixing/reacting a selectively protected and activated drug with a solution of 2-((2-aminoethyl)dithio)ethyl nitrate (LI-5) in a suitable solvent in presence of a suitable coupling agent and/or base.

Another embodiment of the invention is a process for preparation of mutual prodrugs of compounds of formula (I), or pharmaceutically acceptable salts thereof, wherein a process comprises,

A) monoprotection of Bis-(2-hydroxyethyl)disulphide (SL-I) with an appropriate hydroxyl protecting group to give the corresponding monoprotected intermediate LI-Ix, B) reaction of formyl linker intermediate LI-Ixy with amino or hydroxyl containing drug (D l) to obtain the prodrug of formula I with free hydroxyl group on the linker, C) conversion of the intermediate obtained in the step B into activated formyl halide or imidazolide derivative, and

D) reaction of the intermediate obtained in the step C with the drug D^2 to obtain the mutual prodrug of formula I.

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Further embodiments of the invention are processes for the preparation of compounds of formula I, or pharmaceutically acceptable salts thereof, wherein the processes comprise of the steps that are generally depicted in the schemes 1-23.

Further embodiments include the pharmaceutical composition comprising a therapeutically effective amount of novel intermediates or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.

Another embodiment of the invention is use of compounds of formula (I) or pharmaceutically acceptable salt thereof, in the treatment of disease conditions originally treatable by the corresponding free drug(s).

It should be understood that while this invention has been described herein in terms of specific embodiments set forth in detail, such embodiments are presented by way of illustration of the general principles of the invention, and the invention is not necessarily limited thereto. Certain modifications and variations in any given material, process step or chemical formula will be readily apparent to those skilled in the art without departing from the true spirit and scope of the present invention, and all such modifications and variations should be considered within the scope of the claims that follow. The contents of the articles, patents, and patent applications, and all other documents mentioned or cited herein, are hereby incorporated by reference in their entirety to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

Yet another embodiment of the invention is a compound of formula I containing an amino-containing therapeutic agent selected from the group consisiting of: I-AA-MPD1, I-AA-MPD2, 1-AA-MPD3, and I-AA-MPD4.

Another embodiment of the invention is double prodrug of formula (I) selected from the group consisting of: I-AA-MPD5, 1-AA-MPD6, 1-AA-MPD7, and I-AA-MPD8.

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The present invention also provides mutual prodrugs of formula (I) selected from the group consisiting of: I-CA-MPD1, I-CA-MPD2, I-CA-MPD3, I-CA-MPD4, I-CA-MPD5, I-CA-MPD6, I-CA-MPD7, I-CA-MPD8, I-CA-MPD9, I-CA-MPD10, I-CA-MPD11, I-CA-MPD12, I-CA-MPD13, I-CA-MPD14, I-CA-MPD15, I-CA-MPD16, I-CA-MPD17, I-CA-MPD18, I-CA-MPD19, I-CA-MPD20, I-CA-MPD21, I-CA-MPD22, I-CA-MPD23, I-CA-MPD24, I-CA-MPD25, I-CA-MPD26, I-CA-MPD27, I-CA-MPD28, 1-CA-MPD29, and I-CA-MPD30.

In another embodiment, the invention provides compounds of formula (I) selected from the group of mutual prodrugs made from amino-containing therapeutic agent and a hydroxyl-containing therapeutic agent such as: I-AH-MPD1, 1-AH-MPD2, 1-AH-MPD3, I-AH-MPD4, I-AH-MPD5, I-AH-MPD6, I-AH-MPD7, I-AH-MPD10, I-AH-MPD11, 1-AH-MPD12, 1-AH-MPD13, I-AH-MPD14, 1-AH-MPD15, I-AH-MPD16, I-AH-MPD17, I-AH-MPD18, I-AH-MPD19, I-AH-MPD20, I-AH-MPD21, 1-AH-MPD22, 1-AH-MPD23, 1-AH-MPD24, 1-AH-MPD25, and I-AH-MPD26.

Yet another embodiment of the invention relates to compounds of formula (I) of mutual prodrugs made from a hydroxyl-containing therapeutic agent and a hydroxyl-containing therapeutic agent such as: I-HH-MPD1, I-HH-MPD2, I-HH-MPD3, I-HH-MPD4, I-HH-MPD5, I-HH-MPD6, I-HH-MPD7, I-HH-MPD8, I-HH-MPD9, I-HH-MPD10, I-HH-MPD11, I-HH-MPD12, I-HH-MPD13, I-HH-MPD14, I-HH-MPD15, I-HH-MPD16, I-HH-MPD17, and I-HH-MPD18.

The present invention also provides compounds of formula (I) containing water-soluble prodrugs of insoluble or sparingly-soluble therapeutic agents such as: I-H1-PD1, I-H1-PD2, 1-H1-PD3, I-H1-PD4, 1-H1-PD5, 1-H1-PD6, I-H1-PD7, I-H1-PD8, I-H1-PD9, I-H1-PD10, I-H1-PD11, I-H1-PD12, I-H1-PD13, I-A1-PD1, I-A1-PD2, I-A1-PD3, I-A1-PD4, I-A1-PD5, I-A1-PD6, I-A1-PD7, I-A1-PD8, I-A1-PD9, I-A1-PD10, I-A1-PD11, I-A1-PD12, I-A1-PD13, I-A1-PD14, I-A1-PD15A, I-A1-PD16a, I-A1-PD15B, I-A1-PD15B, I-A1-PD16

PD 15Bb, 1-A1-PD16, I-A1-PD17, I-A2-PD1, I-A2-PD2, I-A2-PD2b, I-A2-PD3a, I-A2-PD3b, I-A2-PD4, I-A2-PD5, 1-A3-PD1, 1-A3-PD2a, I-A3-PD2b, I-A3-PD3a, I-A3-PD3b, I-A3-PD4, I-A3-PD5, I-A3-PD6, I-A3-PD7b, I-H1-PD1, I-H1-PD2, I-H1-PD3, I-H1-PD4, I-H1-PD5, I-H1-PD6, I-H1-PD7, I-H1-PD8, I-H1-PD9, I-H1-PD10, I-H1-PD11, I-H1-PD12, I-H1-PD13, I-Taxol-PD1, I-Taxol-PD2, I-Taxol-PD3, I-Taxol-PD4, I-Taxol-PD5, I-Taxol-PD6, and I-S23-PD1.

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Another embodiment of the invention relates to the compounds of formula (1), selected from the group of NO-releasing prodrugs consisting of: I-Cl -NOPDl, I-Cl-NOPD2, 1-Cl-NOPD3a, I-Cl-NOPD3b, I-Cl-NOPD4, 1-Cl-NOPD5a, I-Cl-NOPD5b, C1-NOPD6, 1-C1-NOPD7, 1-C1-NOPD8a, 1-C1-NOPD8b, 1-C1-NOPD9, 1-C1-NOPD10, I-Cl-NOPDlla. I-C1-NOPD13, 1-Cl-NOPD14a, I-Cl-NOPD14b, I-Cl-NOPD15b, I-Cl-NOPD 16, I-CI -NOPD 17a, I-CI -NOPD 17b, I-C1-NOPD18, I-C1-NOPD19, I-Cl-NOPD20a, I-Cl-NOPD20b, I-C1-NOPD21, I-C1-NOPD22, I-Cl-NOPD23b, I-Cl-NOPD24, I-C1-NOPD25, I-C1-NOPD26, I-A1-NOPD1, I-A1-NOPD2, I-A1-NOPD3A, I-A1-NOPD4, I-A1-NOPD5, I-A1-NOPD6, I-A1-NOPD7, I-Al-I-A1-NOPD3B, NOPD8, I-A1-NOPD9, I-Al-NOPDlOa, I-Al-NOPDIOb, I-A2-NOPDla, I-A2-NOPDIb, I-A2-NOPD2a, I-A2-NOPD2b, I-A3-NOPDla, I-A3-NOPDlb, I-A3-NOPD2a, I-A3-NOPD2b, I-H1-NOPD1, 1-H1-NOPD2a, I-H1-NOPD2b, I-H1-NOPD3, I-H1-NOPD4, I-H1-NOPD5b, I-H1-NOPD6, I-H1-NOPD7, I-H1-NOPD8, I-H1-NOPD9, I-H1-NOPD10.

Another aspect of the invention provides the use of the compounds of formula (I) in combination with a compound used to treat cardiovascular diseases selected from the group consisting of: beta adrenergic blockers, calcium channel blockers, angiotensin II receptor antagonists, antithrombotics, HMGCoA reductase inhibitors, aspirin or nitrooxy derivatives of aspirin, nitrosated beta blockers, nitrosated or nitrosilated calcium channel blockers. Suitable drugs are described in the literature such as the Merck Index, IDdb, Prous Science's Integrity[®], Prous Science Drugs of the FutureTM, The Ensemble[®] and the like.

Another aspect of the invention provides the use of the pharmaceutical compositions containing compounds of formula (I) in combination with a compound, used to treat other diseases such as cardiovascular diseases, selected from beta adrenergic blockers, calcium channel blockers, angiotensin II receptor antagonists, antithrombotics,

HMGCoA reductase inhibitors, aspirin or nitrooxy derivatives of aspirin, nitrosated beta blockers, nitrosated or nitrosilated calcium channel blockers. Pharmaceutical compositions containing two or more of compounds of the invention can be used for the purpose of combination therapy. These pairs of compounds of invention can be from the same therapeutic area or from different therapeutic areas for treating one or more diseases or conditions.

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The compounds of the invention, which have one or more asymmetric carbon atoms, can exist as the optically pure enantiomers, pure diastereomers, enantiomer racemic mixtures, diastereomer racemic mixtures, racemates or racemate mixtures. Within the scope of the invention are also all the possible isomers, stereoisomers and their mixtures of the compounds of formula (I).

Another embodiment of the invention relates to the pharmaceutical composition comprising one or more compounds of formula (I) or pharmaceutically acceptable salts thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.

Another embodiment of the invention relates to the pharmaceutical composition comprising one or more compounds of formula (I) or pharmaceutically acceptable salts thereof and at least another pharmaceutically active compound. The pharmaceutically active compound can be from the same or different therapeutic areas for treating one or more disease condition(s) together with one or more pharmaceutically acceptable carriers, vehicles or diluents.

Further embodiments include methods of use of compounds of formula (I) or pharmaceutically acceptable salts thereof.

Another embodiment of the invention is a process for preparation of compounds of formula (I) or pharmaceutically acceptable salts thereof, wherein the process comprises, mixing a selectively protected and activated drug with a solution of 2-((2-hydroxyethyl)dithio)ethyl nitrate in a suitable solvent in presence of a suitable coupling agent. Another embodiment of the invention is a compound or intermediate generated in the above methods and processes.

Another embodiment of the invention is a process for preparation of compounds of formula (I) or pharmaceutically acceptable salts thereof, wherein a process comprises, converting 2-((2-hydroxyethyl)dithio)ethyl nitrate into its formyl halide or imidazolide by

using a phosgene or its equivalent reagent and mixing/reacting the resulting reactive intermediate with a suitable drug in suitable solvent in presence of a suitable base.

Another embodiment of the invention is a process for preparation of compounds of formula (I) or pharmaceutically acceptable salt thereof, wherein the process comprises, mixing/reacting a selectively protected and activated drug with a solution of 2-((2-aminoethyl)dithio)ethyl nitrate (or its acid salt) in a suitable solvent in presence of a suitable coupling agent and/or base.

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Another embodiment of the invention comprises the novel intermediates formed in the preparation of present invention. Further embodiments include a pharmaceutical composition comprising a therapeutically effective amount of novel intermediates or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.

Another embodiment of the invention is processes for the preparation of compounds of formula (I) or pharmaceutically acceptable salt thereof, as well as the starting materials and intermediates involved as depicted in schemes 1-23.

Another embodiment of the invention the novel intermediates obtained in the preparation of compounds of formula I, wherein the intermediates are selected from:

2-((2-Hydroxyethyl)disulfanyl)ethyl acetate (LI-1a)

2-((2-(Trityloxy)ethyl)disulfanyl)ethanol (LI-1c)

2-((2-Hydroxyethyl)disulfanyl)-ethyl nitrate (LI-2b)

2-((2-Hydroxyethyl)disulfanyl)ethyl nitrate (LI-2c.TFA)

tert-Butyl 2-((2-bromoethyl)-disulfanyl)ethylcarbamate (LI-2e)

1,2-Bis(2-bromoethyl)disulfane (LI-3a)

$$LG$$
 O
 S
 S
 NO_2

2-((2-Aminoethyl)disulfanyl)ethyl nitrate.acid salt (LI-5.TFA)

2-((2-(Tetrahydro-2*H*-pyran-2-yloxy)ethyl)disulfanyl)ethanol (**LI-1b**)

$$\mathsf{HO} \overset{\mathsf{S}}{\searrow} \mathsf{S} \overset{\mathsf{O}}{\bigvee} \mathsf{Cl}$$

2-((2-Hydroxyethyl)disulfanyl)ethyl 2-chloroacetate (**LI-1d**)

2-((2-Bromoethyl)disulfanyl)ethanol (LI-2a)

tert-Butyl 2-((2-hydroxyethyl)disulfanyl)ethylcarbamate (LI-2c)

2-((2-(tert-Butoxycarbonylamino)ethyl)-disulfanyl)ethyl methanesulfonate (LI-2d)

tert-Butyl 2-((2-(nitrooxy)ethyl)-disulfanyl)ethylcarbamate (LI-2f)

$$O_2N_O$$
 S_S
 O_{NO_2}

2,2'-Disulfanediylbis(ethane-2,1-diyl) dinitrate (LI-3b)

2-((2-Aminoethyl)disulfanyl)ethyl nitrate (LI-5)

2-((2-Bromoethyl)disulfanyl)ethyl carbonochloridate (LI-6)

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2-((2-((2,5-Dioxopyrrolidin-1-yloxy)carbonyloxy)ethyl)-disulfanyl)ethyl 2-(dimethylamino)ethylcarbamate (LI-IO)

Another embodiment of the invention is use of compounds of formula (I) or pharmaceutically acceptable salts thereof, in the treatment of disease conditions originally treatable by the corresponding free drugs.

Another embodiment of the invention includes but not limited to a pharmaceutical composition comprising the compounds of formula (I), or pharmaceutically acceptable salt thereof, selected from the group of NO-releasing prodrugs described herein, or more pharmaceutically acceptable carriers, vehicles or diluents.

It should be understood that while this invention has been described herein in terms of specific embodiments set forth in detail, such embodiments are presented by way of illustration of the general principles of the invention, and the invention is not necessarily limited thereto. Certain modifications and variations in any given material,

process step or chemical formula will be readily apparent to those skilled in the art without departing from the true spirit and scope of the present invention, and all such modifications and variations should be considered within the scope of the claims that follow. The contents of the articles, patents, and patent applications, and all other documents mentioned or cited herein, are hereby incorporated by reference in their entirety to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

POTENTIAL EXAMPLES OF MUTUAL PRODRUGS/CODRUGS:

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Mutual prodrugs made from an amino-containing therapeutic agent and another amino-containing therapeutic agent:

A Mutual Prodrug of desloratadine and pseudoephedrine (I-AA-MPD1) is proposed as a potential treatment option for seasonal allergic rhinitis (SAR). Desloratadine (an active metabolite of loratadine) is a new, non-sedating, long-acting histamine antagonist and has been shown effective in the treatment of nasal and non-nasal symptoms associated with SAR. Pseudoephedrine is an oral decongestant.

A Mutual Prodrug of amlodipine (Pfizer's Norvasc®) and lisinopril (Zeneca's Zestril®) (I-AA-MPD2) is proposed as a potential treatment option for hypertension and congestive heart failure. Amlodipine is a calcium channel blocker and is used as an antihypertensive and antianginal agent. Lisinopril is an angiotensin-converting enzyme (ACE) inhibitor and is used for the treatment of hypertension and congestive heart failure. A combination therapy using these two drugs has been proven to be more effective treatment option than monotherapy using either of these drugs.

A Mutual Prodrug of amlodipine (Pfizer's Norvasc®) and losartan (Merck's Cozaar®) (I-AA-MPD3a) is proposed as a potential treatment option for mild to moderate hypertension. Amlodipine is a calcium channel blocker and is used as an antihypertensive and antianginal agent. Losartan potassium is an angiotensin II blocker and is used for the treatment of hypertension. A combination therapy using these two drugs has been proven to be more effective treatment option than monotherapy using either of these drugs.

Examples of mutual prodrugs and double prodrugs of valdecoxib and celecoxib containing a disulfide linker are: I-AA-MPD4 and I-AA-MPD5.

Examples of double prodrugs of valdecoxib or celecoxib containing non-disulfide linkers: I-AA-MPD6, 1-AA-MPD7, 1-AA-MPD8.

A Mutual Prodrug of fluoxetine (Lilly's Prozac®) and olanzapine (Lilly's Zyprexa®) (I-AA-MPD9) is proposed for potential treatment of patients with Bipolar disorder. Fluoxetine and Olanzapine are used in combination to treat patients with bipolar disorder while being spared the treatment-emergent mania that such patients often get on antidepressant monotherapy.

Example of double prodrug of gabapentin is proposed as potential antiepileptic agent: I-AA-MPD10.

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$$HO_2C$$
 S O N CO_2H

Mutual prodrugs made from an amino-containing therapeutic agent and a carboxyl-containing therapeutic agent:

A mutual prodrug of cetirizine and pseudoephedrine (I-CA-MPD1) is proposed for treatment of rhinitis. Cetirizine is an antihistamine and pseudoephedrine is a nasal decongestant.

Mutual prodrugs of gabapentin and valproic acid are potential antiepileptic agents. This same kind of prodrug may be a potential treatment option for patients with bipolar disorder and other mental illnesses. The following are some of the examples:

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Other illustrative examples of mutual prodrugs under this category include the following: Mutual prodrugs of valproic acid and other carboxyl-, hydroxyl-, and aminocontaining (including amide-, and sulfonamide-containing) anticonvulsant agents such as levetiracetam, lamotrigine, pregabalin, carbamazepine, oxcarbamazepine, licarbazepine, felbamate, topiramate and the like. (Structures are given below). The list also includes investigational antiepileptic agents such as antipamezole, licarbazepine, Eslicarbazepine Acetate (BIA 2-093), fluorofelbamate, isovaleramide (NPS 1776), retigabine (D-23129), safmamide (NW-IOI 5), stiripentol (STP), talampanel (TLP), (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl]butanamide 83 alpha (ucb 34714), valrocemide (TV 1901), and the like.

Mutual Prodrugs can be made from combination of any two anti-convulsant agents listed above or any other suitable anticonvulsant agents.

Mutual prodrug of gabapentin and naproxen (I-CA-MPD22) is proposed for potential treatment option for neurological pain and inflammation.

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Mutual prodrugs made from an amino-containing therapeutic agent and a hydroxyl-containing therapeutic agent:

Mutual prodrugs of norfloxacin and metronidazole (I-AH-MPD1, 1-AH-MPD2, 1-AH-MPD3) are proposed for potential treatment of diarrhea and dysentery of bacterial, amoebic and mixed origin. Metronidazole is an antianaerobic agent and used in combination with antibiotics such as norfloxacin, ciprofloxacin, etc. for the treatment of patients with diarrhea and dysentery of bacterial, amoebic and mixed origin.

A mutual prodrug of loperamide and.norflaxacin (I-AH-MPD4) is proposed for potential treatment of diarrhea and dysentery.

A mutual prodrug of valdecoxib and tramadol (I-AH-MPD5 and I-AH-MPD6) as a potential therapy in postoperative pain management.

A mutual prodrug of gabapentin and tramadol (I-AH-MPD7) is proposed for potential treatment of neuropathic pain after spinal cord injury.

A mutual prodrug of venlafaxine and paroxetine (I-AH-MPD8) is proposed for potential treatment of neurological and depression related disorders.

Mutual prodrugs made from a hydroxyl-containing therapeutic agent and another hydroxyl-containing therapeutic agent:

Mutual prodrugs of zidovudine (AZT/Retrovir) and lamivudine (3TC/Epivir) (I-HH-MPDl, I-HH-MPD2) are proposed as a potential treatment option for HIV and other viral infections.

POTENTIAL EXAMPLES OF WATER-SULUBLE PRODRUGS:

Water-soluble prodrugs of insoluble/sparingly-soluble therapeutic agents can be prepared using the same linker technology.

Water-soluble prodrugs of metronidazole include: I-H1-PD-2, I-H1-PD-3, I-H1-PD-4.

Water-soluble prodrugs of valdecoxib include: I-A3-PD1, I-A3-PD2a, I-A3-PD2b, I-A3-PD3a, I-A3-PD3b, I-A3-PD4, 1-A3-PD5, 1-A3-PD6, and I-A3-PD7b.

Water-soluble prodrugs of paclitaxel include: I-Taxol-PDI, I-Taxol-PD2, 1-Taxol-PD3, 1-Taxol-PD4, 1-Taxol-PD5, 1-Taxol-PD6, and I-S23-PD1.

30 POTENTIAL EXAMPLES OF NO-RELEASING PRODRUGS:

In the following potential examples, X is O, NR¹ (R¹= H, alkyl) or a bond; Y is CO, SO₂, PC=O)XR¹ or bond; R¹ is H, alkyl, aralkyl, or a metal ion; A is a bond, 1,4-/1,3-/1,2-phenylene or (CH₂)_O($^{\circ}$ = 0-6) and m is 1-2 unless otherwise stated;

Prodrugs of Valproic Acid (Anticonvulsant):

DRUGS CONTAINING REACTIVE PRIMARY AND SECONDARY AMINES, AMIDE-NH, UREA-NH, SULFONAMIDE-NH, SULFAMATE-NH, AND CARBAMATE-NH:

 $Prodrugs\ of\ Gabapentin\ \ (Anticonvulsant):$

(Anticonvulsant):

Prodrugs of Carbamazepine (Anticonvulsant):

NO-Releasing Prodrugs of Paracetamol/Acetaminophen (Analgesic and Antipyretic):

ADDITIONAL POTENTIAL EXAMPLES:

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In the following additional potential examples, X is O, NR¹ (R¹= H, alkyl) or a bond; Y is CO, SO₂, PC=O)XR¹ or bond; R¹ is H, alkyl, aralkyl, or a metal ion; A is a bond, 1,4-/1,3-/1,2-phenylene or $(CH_2)_0$ (o = 0-6) and m is 1-2 unless otherwise stated;

NO-Releasing Prodrugs of Nicotinamide:

NO-Releasing Prodrugs of NSAIDs:

NO-Releasing Prodrugs of Aspirin

NO-Releasing Prodrugs of Paracetamol

NO-Releasing Prodrugs of Mesalamine

NO-Releasing Prodrugs of Naproxen

NO-Releasing Prodrugs of Flurbiprofen

NO-Releasing Prodrugs of Ketoprofen

NO-Releasing Prodrugs of Indomethacin

NO-Releasing Prodrugs of Ibuprofene

NO-Releasing Prodrugs of Ketorolac

NO-Releasing Prodrugs of Diclofenac

NO-Releasing Prodrugs of Glucocorticoids:

NO-Releasing Prodrug of Prednisolone

NO-Releasing Prodrug of Ursodeoxycholic Acid

NO-Releasing Prodrug of Hydrocortisone

NO-Releasing Prodrug of Budesonide

NO-Releasing Prodrugs of Antioxidants and /or Free Radical Scavengers:

NO-Releasing Prodrug of TEMPOL (4-hvdroxy-TEMPO):

NO-Releasing Prodrugs of Probucol and AGI-1067:

NO-Releasing Prodrugs of Vitamin E (alfa-tocopheroD:

NO-Releasing Prodrugs of Edaravone (3-methyl-1-phenyl-2-pyrazolin-5one):

NO-Releasing Prodrugs of Antibiotics:

NO-Releasing Prodrugs of Metronidazole

$$\begin{array}{c} NO_2 \\ N \\ CH_3 \\ NO_2 \\ N \\ NO_2 \\ N \\ NO_2 \\ NO_3 \\ NO_3 \\ NO_4 \\ NO_4 \\ NO_5 \\ NO_$$

NO-Releasing Prodrugs of Norfloxacin:

NO-Releasing Prodrugs of Antiepileptic Agents:

NO-Releasing Prodrugs of Valproic Acid

NO-Releasing Prodrug of Gabapentin

$$H_{3}C$$
 $H_{3}C$
 H

NO-Releasing Prodrug of Levetiracetam

NO-Releasing Prodrug of Lamotrigine

$$\begin{array}{c} CI \\ CI \\ N_{N} \\ N_{N}$$

NO-Releasing Prodrug of Carbamazepine

5 Plausible Mechanisms of Drug Release from Prodrugs

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Drugs can be released form the prodrugs and mutual prodrugs via cleavage of biolabile linker(s) in vivo (cleavage can be either chemical or enzymatic or both) by illustrative mechanisms as shown in Schemes M1 through M5.

Plausible mechanisms for concomitant release of nitric oxide (NO) and free drug from NO-releasing prodrug(s) of amino-, hydroxyl-, or carboxyl-containing drug(s) are illustratively shown in Schemes M1. Thus, the attack of thiolate ion (from GSH or any other sulfahydryl-containing species) on nitrooxy-containing prodrug would release carboxylic acid-containing free drug, episulfide (d) and the intermediate conjugate (a) according to path 1. If the prodrugs are made from amino-, or hydroxyl-containing drugs, then the prodrug would be cleaved via path 2 to release the corresponding free drug, the cyclic thiocarbonate intermediate (c) and the intermediate conjugate (a). The cyclic thiocarbonate intermediate may further breakdown into episulfide (d) and carbon dioxide. The reactive episulfide (d) would be further neutralized by glutathione. The nitrate ester-containing intermediate conjugate can further break down in the presence of GSH to glutathione dimer (GS-SG) and transient intermediate (b), which can break down via path

3 to release NO. It is also possible the same transient intermediate can break down via path 4 to yield episulfide (d) and a relatively innocuous nitrate anion (NO₃7).

X = O, NR^1 ($R^1 = H$ or alkyl or a group linked to the drug) or a bond

Scheme M1

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Plausible mechanisms of drug release from mutual prodrugs of one carboxyl-containing and one amino-/hydroxyl-containing drug is shown in Scheme M2.

Plausible mechanism of drug release from prodrugs (including mutual and NO-releasing prodrugs of amino-, hydroxyl-and carboxyl-containing drugs) containing modified bio-labile linkers is shown in Scheme M3. Thus, the thiolate anion derived from the attack of glutathione on disulfide of the prodrug may trigger cyclization to release the free drug (Dl-X mlH) and a stable six-membered (or five-membered, if X p2 is a bond) thio-lactone intermediate.

Prodrug

 D^1 , D^2 and L^2 are as defined in the text.

 $X^{ml} = O$, NR1 (R = a bond, H, alkyl, or a metal ion), CONR , SO_2NR^1 , $P(O)NR^1$, OC(O)NR , OSO2NRWd the like.

 X^{m2} is a bond, CH_2 , O, $NR^{m1}(R^{m1}$ is H, alkyl, aryl or a bond), S, SO, SO_2 and the like

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Releases the second drug or NO or promoiety via plausible mechanisms as shown in Schemes M1and M2 Scheme M3

Plausible mechanisms of drug release from double/mutual prodrugs containing additional linkages to couple two hydroxyl-containing drugs are shown in Scheme M4. Thus, the thiolate anion generated by the attack of glutathione on disulfide bond of the prodrug triggers further cleavage as shown to release the free drug (D'-OH) and a five-membered 2-imidazolidone. Through in vitro decomposition studies, we have found that the drug release from this type of prodrug is more facile when R group is an alkyl group.

This invention also covers novel bio-labile linkers containing 1,4-phenylene group and 1,2-phenylene group as shown in Schemes 5 and 6, respectively. As depicted in Scheme M5, the linker is expected to release the free Drug¹ upon glutathione-assisted cleavage and may generate 1,4-quinonemethid (ea) as a byproduct via 1,6-elimination process. Similarly, the free Drug² is expected to be released from the intermediate conjugate (a) as shown in the scheme.

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Scheme M5

As depicted in Scheme M6, the 1,2-phenylene-containing linker is also expected to release free drugs upon glutathione assisted cleavage and genereate 1,2-quinonemethid (eb) as a byproduct via 1,4-elimination process (via pathway 'b'). However, this linker can also cleave via pathway 'a' to generate benzo-monothiocarbonate as a byproduct.

Although the generated byproducts seem to be toxic, they are likely to be quickly neutralized by detoxification enzymes in the body.

Scheme M7: Plausible mechanism of diazepam formation from an acyclic prodrug of diazepam

Water-soluble acyclic prodrug design for Diazepam

Diazepam, a benzodiazepine tranquilizer, is very sparingly water-soluble drug and a water-soluble acyclic prodrug of diazepam can be made by using our linker technology. As shown in the Scheme M7, reduction of disulfide bond in the prodrug triggers release of open-chain intermediate of diazepam which spontaneously cyclizes to diazepam *in vivo*.

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Where GSH is glutathione (reduced) or any other in vivo bioreductive agent that can reduce the disulfide bond. As illustrated, cleavage of disulfide bond triggers further breakage of the remaining portion of the linker to release the free drugs. In the process, some byproducts are generated and these are either eliminated or further degraded by some biological process. For clarity, the mechanism of cleavage of the linker is shown as occurring in stepwise manner. However, both the steps can possibly occur in a concomitant fashion to release both the drugs simultaneously.

As illustrated in Scheme M3 and M4, Linkers may have additional spacer groups between one side (or both sides) of the linkers and the drug molecule and some of these spacer groups may be cleaved independently by a chemical or enzymatic process to release the drugs prematurely before the cleavage of disulfide linkage. The prodrugs and mutual prodrugs containing such spacer groups may be useful when faster release of drug(s) is desired.

LISTS OF CANDIDATE DRUGS USEFUL FOR PRODRUG SYNTHRSTS:

Drugs listed in the following list can be converted to NO- releasing prodrugs. This list is in no way limiting the scope of drugs covered in this invention, but given as representative examples. All the amino- (including amide-NH and sulfonamide-NH, carbamate-NH, sulfamate-NH, hydrazone-NH, semicarbazone-NH, thiosemicarbazone-NH, urea-NH, phosphoramide-NH and the like. See above, for the description of "amino-containing drugs"), carboxyl-, hydroxyl-(including oxime-OH), and carbonyl (both aldehyde and keto groups)-containing drugs under various therapeutic categories as listed in Merck Index (13th editions) and other data bases such as prous science's ensemble, integrity, and the like and also all the qualified (i.e., amino-, and /or hydroxyl-, and/or carboxyl-, and/or carbonyl-containing) investigational drugs as listed in databases such Merck Index (13th editions), iddb, ensemble, integrity, and the like, are covered under this invention without any limitation.

ANTI-INFLAMMATORY DRUGS:

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Amino-containing (including Amide NH and Sulphonamide NH and Phosphomide NH, etc.): Ampiroxicam, Bucolome, Celecoxib, Difenpiramide, Mofebutazone, Nimesulide, Paranyline, Parecoxib, Parsalmide, Piketoprofen, Talniflumate, Tenidap, Terofenamate, and Valdecoxib.

Hydroxyl-containing: 21-Acetoxypregnenolone, Alclometasone, alfa-Bisabolol, Budesonide, Deflazacort, Diflorasone, Desonide, Desoximetasone, Diflorasone, Diflucortolone, Difluprednate, Ditazol, Fluazacort, Fluocinonide, Fluocortin Butyl, Fluprednidene Acetate, Glucametacin, Halcinonide, Halobetasol Propionate, Halometasone, Halopredone Acetate, Ibuproxam, Loteprednol Etabonate, Mazipredone, Mometasone Furoate, Oxyphenbutazone, Perisoxal, Rimexolone,

Hydroxyl-, and Amino-containing (including Amide NH and Sulphonamide NH and Phosphomide NH, etc.): Bufexamac, Etofenamate, Fepradinol, Ibuproxam, Isoxicam, Lornoxicam, Meloxicam, Oxametacine, Piroxicam, and Tenoxicam.

Hydroxyl- and sulphahydryl-containing: Tixocortol,

Carboxyl- and Amino-containing (including amide NH and sulphonamide NH and phosphomide NH, etc.): Aceclofenac, Alminoprofen, Amfenac, 3-Amino-4-

hydroxybutyric Acid, Carprofen, Diclofenac, Enfenamic Acid, Etodolac, Flufenamic Acid, Meclofenamic Acid, Mefenamic Acid, Niflumic Acid, and Tolfenamic Acid.

Carboxyl-containing: Acemetacin, Acetamidocaproic Acid, Bendazac, Benoxaprofen, Beπnoprofen, Bucloxic Acid, Butibufen, Cinmetacin, Clidanac, Clopirac, Felbinac, Fenbufen, Fenclozic Acid, Fenoprofen, Fentiazac, Flunoxaprofen, Flurbiprofen, Ibuprofen, Indomethacin, Isofezolac, Isoxepac, Ketoprofen, Lonazolac, Loxoprofen, Metiazinic Acid, Mofezolac, Naproxen, Oxaprozin, Pirazolac, Pirprofen, Pranoprofen, Protizinic Acid, Sulindac, Suprofen, Suxibuzone, Tiaprofenic Acid, Tolmetin, and Tropesin.

10 Carboxyl- and Hydroxyl-containing: Balsalazide, Enoxolone, Fendosal, Olsalazine, Oxaceprol, and Ximoprofen.

Amino-, Carboxyl- and Hydroxyl-containing: 3-Amino-4-hydroxybutyric Acid, Mesalamine, and Sulfasalazine.

Keto-containing: Nabumetone, and Piketoprofen.

Carboxyl- and keto-contianing: Bermoprofen, Bucloxic Acid, Isoxepac, Ketoprofen, Loxoprofen, and Zaltoprofen.

ANALGESIC AND/OR ANTIPYRETIC DRUGS:

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Amino-containing: Aminochlorthenoxazin, Aminopropylon, Anileridine, Antrafenine, Benorylate, Benzpiperylon, p-Bromoacetanilide, Butacetin, Carsalam, Difenamizole, Etersalate, Ethenzamide, Ethoxazene, Flipirtine, Isonixin, Nifenazone, Phenacetin, Phenazopyridine, Phenocoll, Phenopyrazone, Piminodine, Piritramide, Propacetamol, Ramifenazone, Piperylone, Salverine, and Tinoridine.

bis(acetylsalicylate), Benzylmo \phi hine, Hydroxyl-containing: Aluminum Bupreno φ hine, Butorphanol, Chlorobutanol, Ciramadol, Codeine, Desomo φ hine, Dihydrocodeine, Dihydromorphine, Dihydroxyaluminum acetylsalicylate, Dimepheptanol, Eptazocine, Ethylmorphine, Eugenol, Hydroxypethidine, Levo¢ hanol, Meptazinol, Metazocine, Moo hine, Nalbuphine, Pentazocine, Phenazocine, Phenoperidine, Phenylsalicylate, Salicin, Tramadol, and Viminol.

Carboxyl-containing: Acetylsalicylsalicylic acid, Alclofenac, Aspirin, 30 Benoxaprofen, 5-Bromosalicylic acid acetate, Cinchophen, Diacerein, Dipyrocetyl, Fosfosal, Ibufenac, Indoprofen, and Salicysulfuric acid.

Amino- and Hydroxyl-containing: Acetaminophen, Acetaminosalol, Bucetin, Capsaicine, Dezocine, Floctafenine, Glafenine, Isoladol, p-Lactophenetide, Norlevorphanol, Noπnorphine, Phenylramidol, Salacetamide, and Salicylamide.

Amino- and Carboxyl-containing: Actarit, Bumadizone, Clonixin, and Salicylamide O-acetic acid.

Carboxyl- and Hydroxyl-containing: Diflunisal, Gentisic acid, and Salsalate.

Keto-containing: Amtolmetin, Dipipanone, Hydrocodone, Isomethadone, Methadone, Norpipanone, and Phenadoxone.

Hydroxy- and Keto-containing: Hydromorphone, Ketobemidone, Metopon, 10 Oxycodone, and Oxymorphone.

Carboxyl- and Keto-containing: Clometacin, Ketorolac, and Zomepirac.

Amino- Carboxyl- and Keto-containing: Bromfenac.

ANTIHYPERTENSIVE DRUGS:

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Amino-containing: Alfuzosin, Benzylhydrochlorothiazide, Bethanidine, Clopamide, Bunazosin, Ciclosidomine, Clonidine, 15 Bopindolol, Budralazine, Cyclopenthiazide, Debrisoquin, Edeseø idine, Diazoxide, Dihydralazine, Doxazosin, Guanabenz, Guanacline, Guanazodine, Guanethidine, Guanochlor, Endralazine, Guanadrel, Guanfacine, Guanoxan, Hydracarbazine, Hydralazine, Hydroflumethiazide, Lofexidine, Indapamide, Indoramin, Irbesartan, Ketanserin, Mebutamate, Mecamylamine, Methyl 4-pridyl ketone thiosemicarbazone, Mibefradil, Minoxidil, 20 Monatepil, Moxonidine, Pheniprazine, Pinacidil, Prazosin, Raubasine, Rescinnamine, Reserpiline, Reserpine, Rilmenidine, Syrosingopine, Tasosartan, Terazosin, Tiamenidine, Todralazine, Tolonidine, Tripamide, and Urapidil.

Hydroxy-containing: Ajmaline, Cicletanine, Levcromakalim, Naftopidil, Phenactropinium chloride, and Protoveratrines.

Carboxyl-containing: Eprosartan, Fosinopril, and Telmisartan,

Amino- and Carboxyl-containing: Alacepril, gama-Aminobutyric acid, Benazepril, Candesartan, Carmoxirole, Caronapril, Cilazapril, Delapril, Enalapril, Enalaprilat, Imidapril, Lisinopril, Moexipril, Moveltipril, Perindopril, Quinapril, Ramipril, Saralasin, Spirapril, Temocapril, Trandolapril, and Valsartan.

Amino- and Hydroxyl-containing: Acebutolol, Alprenolol, Amosulalol, Arotinolol, Atenolol, Betaxolol, Bisoprolol, Bosentan, Bucindolol, Bufeniode, Bunitrolol, Bupranolol, Butofilolol, Cadralazine, Celiprolol, Carazolol, Carteolol, Cetamolol, Carvedilol, Epanolol, Indenolol, Nadolol, Dilevalol, Fenoldopam, Guanoxabenz, Labetalol, Losartan, Mepindolol, Metipranolol, Metoprolol, Moprolol, Nebivolol, Olmesartan, Oxprenolol, Penbutolol, Phentolamine, Pildralazine, Pindolol, Propranolol, Rescimetol, Sulfinalol, Talinolol, Tertatolol, Timolol, and Trimazosin.

Amino-, Hydroxyl- and Carboxyl-containing: Methyldopa, and Sampatrilat, Sulfahydryl-and Carboxyl-containing: Captopril, and Omapatrilat,

10 Carbonyl-containing: Aranidipine, and Eplerenone,

ANTIBIOTICS:

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All the known amino-, hydroxyl-, and carboxyl-containing antibiotics such as Amoxicillin, Ampicillin, Olivanic acid, Metronidazole, and the like as listed in Merck Index. 13th edition and other drug databases integrity, ensemble, iddb, and the like. These antibiotics can be used in combination with beta-lactamase inhibitor such as clavulanic acid, penicillinic acid sulfone and the like. The following lists of antibacterial and antifungal agnets are given for clarity.

ANTIBACTERIAL AGENTS:

Amino-containing: Acedapsone, Acetosulfone sodium, Ambazone, Bacampicillin, 20 Benzylsulfamide, Brodimoprim, Cefcapene pivoxil, Cefpodoxime proxetil, Chloramine-B, Chloramine-T, Capreomycin, Clofazimine, Cyacetacide, Cycloserine, Dapsone, Ethionamide, Furazolium chloride, N2-Formylsulfisomidme, Furonazide, Isoniazid, Lenampicillin, Linezolide, Mafenide, 4'-(Methylsulfamoyl)sulfanilanilide, Morphazinamide, Nifuradene, Nitrofurantoin, Penamecillin, Penethamate hydriodide, Pexiganan, Pivampicillin, Pivcefalexin, Picloxydine, Protionamide, Pyrazinamide, 25 Solasulfone, Subathizone. 4,4'-Sulfinyldianiline, Sulfoxone sodium, 4'-Sulfabenzamide, Sulfacetamide, Sulfanilylsulfanilamide, Sulfoniazide, Sulfachlorpyridazine, Sulfacytine, Sulfadiazine, Sulfadicramide, Sulfadimethoxine, Sulfadoxine, Sulfaethidole, Sulfaguanidine, Sulfaguanole, Sulfalene, Sulfamerazine, Sulfameter, Sulfamethazine, Sulfamethizole, Sulfamethomidine, Sulfamethoxazole, 30 Sulfamethoxypyridazine, Sulfamethylthiazole, Sulfametrole, Sulfamidochrysoidine,

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Sulfamoxole, Sulfanilamide, p-Sulfanilylbenzylamine, Sulfanilylurea, N-Sulfanily 1-3,4-xylamide, Sulfaperine, Sulfaphenazole, Sulfaproxyline, Sulfapyrazine, Sulfasomizole, Sulfasymazine, Sulfathiazole, Sulfathiourea, Sulfasomidine, Sulfasoxazole, Sulfathiourea, Sulfatolamide, Talampicillin, Taurolidine, Tetroxoprim, Thiazosulfone, Thiacetazone, Tiocarlide, and Trimethoprim.

Hydroxyl-containing: Azithromycin, Chloroxylenol, Chlorquinadol, Clofoctol, Cloxyquin, Diathymosulfone, Glucosulfone sodium, Nifurpirinol, Nifurtoinol, Nitroxoline, Roxarsone, Roxithromycin, Xanthocillin, and Xibornol.

Carboxyl-containing (including sulfate, phosphate and phosphonate-containing):

10 Amdinocillin, Cinoxacin, Difloxacin, Fosfomycin, and Hydnocarpic acid.

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Amino- and Carboxyl-containing (including sulfate-, sulfonic acid-, phosphate and phosphonate-containing): Acediasulfone, Amphomycin, Ampicillin, Azidocillin, Azlocillin, Bacitracin, Balofioxacin, Betamipron, Carbenicillin, Aztreonam, Carindacillin, Carumonam, Cefaclor, Cefazedone, Cefazolin, Cefclidin, Cefditoren, Cefepime, Cefetamet, Cefixime, Cefmenoxime, Cefmetazole, Cefodizime, Ceforanide, Cefotaxime, Cefotetan, Cefotiam, Cefoxitin, Cefozopran, Cefpimizole, Cefpirome, Cefroxadine, Cefsulodin, Ceftazidime, Cefteram, Ceftezole, Ceftibuten, Ceftizoxime, Ceftriaxone, Cefuroxime, Cefuzonam, Cephacetrile sodium, Cephalexin, Cephaloglycin, Cephaloridine, Cephalosporin C, Cephalothin, Cephapirin sodium, Cephradine, Cilastatin, Ciproflaxacin, Clinafioxacin, Clometocillin, Cyclacillin, Dicloxacillin, Enoxacin, Epicillin, Fenbenicillin, Floxacillin, Hetacillin, Loracarbef, Metampicillin, Methicillin, Mezlocillin, Nafcillin, Noprysulfamide, Opiniazide, Oxacillin, Penicillin(s), Penimepicycline, Phenethicillin, Phthalylsulfacetamide, Phthalylsulfathiazole, Piperacillin, Propicillin, Quinacillin, Succinylsulfathiazole, Succisulfone, Sulbenicillin, Sulfachrysoidine, Sulfanilic acid, Temocillin, Ticarcillin, and Tigemonam.

Amino- and Hydroxyl-containing: Amikacin, p-Aminosalicylic acid hydrazide, Arbekacin, Azidamfenicol, Bambermycins, 5-Bromosalicylhydroxamic acid, Butirosin, Clindamycin, Clomocycline, Chloramphenicol, Cloxacillin, Colistin, Demeclocycline, Deoxydihydrostreptomycin, Dibekacin, Dihydrostreptomycin, Dirithromycin, Doxycycline, Enviomycin, Ethambutol, Forimicins, Gentamycin, Glyconiazide, N4-beta-D-Glucosylsulfanilamide, Gramicidin(s), Isepamicin, Kanamycin(s), Lincomycin,

Meclocycline, Methacycline, Micronomicin, Neomycin, Netilmicin, Novobiocin, Paromomycin, Phenyl aminosalicylate, Pipacycline, Polymyxin, Primycin, Ramoplanin, Ribostamycin, Rifabutin, Rifalazil, Rifamide, Rifamycin SV, Rifampin, Rifapentine, Rifaximin, Ristocetin, Salinazid, Sancycline, Sisomicin, Streptolydigin, Streptomycin, Streptonicozid, 2-p-Sulfanilylanilinoethanol, Thiamphenicol, Thiostrepton, Tobramycin, Tuberactinomycin, Viomycin, and Virginiamycin.

Hydroxyl- and Carboxyl-containing (including sulfate, phosphate and phosphonate-containing): Fropenem, Nadifloxacin, Biapenem, Fusidic acid, and Merbromin.

Hydroxyl- and Aldehyde-containing: Josamycin, Leucomycins, Midecamycins, Miokamycin, Rokitamycin, and Spiramycin.

Amino-, Hydroxyl-, and Carboxyl-containing (including sulfate, phosphate and phosphonate-containing): p-Aminosalicylic acid, Apicycline, Amoxicillin, Apalcillin, Aspoxicillin, Benzoylpas, Cefadroxil, Cefamandole, Cefatrizine, Cefbuperazone, Cefdinir, Cefminox, Cefonicid, Cefoperazone, Cefoselis, Cefpiramide, Cefprozil, Ertapenem, Flomoxef, Imipenem, Lymecycline, Meropenem, Moxalactam, Negamycin, Panipenem, Ritipenem, Salazosulfadimidine, Sulfaloxic acid, 4-Sulfanilamidosalicylic acid, Teicoplanin, Tyrocidine, and Vancomycin.

Keto-containing: Troleandomycin.

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Hydroxy- and Keto-containing: Carbomycin, Clarithromycin, Erythromycin, all erythromycin ester derivatives, Oleandomycin, and Telithromycin.

Hydroxy-, Aldehyde-, and Keto-containing: Rosaramicin.

Amino- and Keto-containing: Porfiromycin.

Carboxyl- and Keto-containing: Fleroxacin, Flumequine, Miloxacin, Nalidixic acid, Ofloxacin, Oxolinic acid, Pefloxacin, Piromidic acid, Prulifloxacin, Rosoxacin, and Rufloxacin.

Amino-, hydroxyl-, and Keto-containing: Chlortetracycline, Dalfopristin, Guamecycline, Mikamycin, Minocycline, Oxytetracycline, Pristinamycin, Quinupristin, Rolitetracycline, Spectinomycin, and Trospectomycin.

carboxyl-,and keto-contianing: Garenoxacin, Gatifloxacin, Amino-. Gemifloxacin, Grepafloxacin, Lomefloxacin, Moxifloxacin, Norfloxacin, Pazufloxacin, Pipemidic acid, Sitafloxacin, Sparfloxacin, Tosufloxacin, and Trovafloxacin.

Sulfahydryl-containing: Pyrithione.

5 **ANTIFUNGAL AGENTS:**

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Amino-containing: Chlordantoin, Exalamide, Flucytosine, Loflucarban, Magenta I, and Pyrrolnitrin.

Filipin, Hydroxy-containing: Chloo henesin, Ciclopirox, Dermostatin, Fluconazole, Fungichromin, Pecilocin, Posaconazole, Ravuconazole, Rubijervine, Siccanin, 2,4,6-Tribromo-m-cresol and Voriconazole.

Carboxyl-containing: Undecylenic acid (10-undecenoic acid), and Propionic acid,

Amino- and Carboxyl-containing: Azaserine.

Amino- and Hydroxyl-containing: Salicylanilide, Acrisorcin (9-Aminoacrindine compound with 4-Hexylresorcinol (1:1)), Anidulafungin, Bromosalicylchloranilide, Buclosamide, Caspofungin, Micafungin, and Tubercidin.

Amino-, Carboxyl- and Hydroxyl-containing: Natamycin, Amphotericin B, Lucensomycin, and Nystatin.

Carbonyl-containing: sodium propionate and griseofulvin.

Hydroxy- and carbonyl-containing: Viridin. 20

Amino-, hydroxyl-, and carbonyl-containing: Perimycin and Mepartricin.

Amino-, carboxyl-, hydroxyl-, and carbonyl-containing: Candicidin.

ANTIVIRAL DRUGS:

Hydroxy-containing: Edoxudine, Floxuridine, Idoxuridine, Kethoxal, Podophyllotoxin, Sorivudine, Stavudine, Trifluridine, and Zidovudine.

Amino-containing: Amantadine, Amidinomycin, Atevirdine, Capravirine, Delavirdine, Efavirenz, Famciclovir, Imiquimod, Lamivudine, Methisazone, Moroxydine, Nevirapine, Oseltamivir, Rimantadine, Stallimycin, mantadine, and Valacyclovir.

Amino- and Hydroxyl-containing: Abacavir, Acyclovir, Adefovir, Amprenavir, 30 Atazanavir, Cidofovir, Didanosine, Dideoxyadenosine, Emtricitabine, Entecavir, Indinavir, Lamivudine, Lopinavir, 5-(methylamino)-2-deoxyuridine (MADU), Nelfinavir, Penciclovir, Resiquimod, Ribavirin, Ritonavir, Saquinavir, Tenofovir, Tipranavir, Valganciclovir, Vidarabine, and Zalcitabine.

Carboxyl- and Hydroxyl-containing: Foscarnet sodium, and Ganciclovir.

Amino-, Carboxyl- and Hydroxyl-containing: Zanamivir.

ANTIMALARIAL:

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Amino-containing: Chlorguanide, Chloroquine, Chlorproguanil, Cycloguanil, Pamaquine, Plasmocid, Primaquine, Quinocide, and Tafenoquine.

Hydroxyl-containing: Artemisinin alcohol, Bebeerines, Cinchonidine,

10 Cinchonine, Dihydroartemisinin, Halofantrine, Lumefantrine, Quinine and Yingzhaosu

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Carboxyl-containing: Arteflene and Artesunate.

Amino-, and Hydroxyl-containing: Amodiaquin, Hydroxychloroquine, Mefloquine, and Pyronaridine.

Hydroxyl, and carbonyl-containing: Fosmidomycin.

Carbonyl-containing: Arteflene.

ANTINEOPLASTIC DRUGS:

Hydroxy-containing: Aclacinomycins, Arzoxifene, Batimastat, Broxuridine, Calusterone, Capecitabine, CC-1065, Chromomycins, Diethylstilbestrol, Docetaxel, Doxifluridine, Droloxifene, Dromostanolone, Enocitabine, Epitiostanol, Estramustine, Etanidazole, Etoposide, Fenretinide, Flavopiridol, Formestane, Fosfestrol, Fulvestrant, Gemcitabine, Irinotecan, Melengestrol, Menogaril, Miltefosine, Mitobronitol, Mitolactol, Mopidamol, Nitracrine, Nogalamycin, Nordihydroguaiaretic Acid, Olivomycins, Paclitaxel and other known paclitaxel analogs, Plicamycin, Podophyllotoxin, Retinoic acid (including all trans-retinioc acid), Roquinimex, Rubitecan, Seocalcitol, Temoporfin, Teniposide, Tenuazonic Acid, Topotecan, Valrubicin, Vinblastine, Vincristine, and Zosuquidar.

Amino-containing (including Amide-NH and Sulphonamide-NH, Carbamate-NH, Sulfamate-NH, and Phosphomide-NH): 9-Aminocamptothecin, Aminolevulinic Acid, Amsacrine, Bisantrene, Cactinomycin, Carboquone, Carmofur, Carmustine, Cyclophosphamide, Dacarbazine, Dactinomycin, Demecolcine, Diaziquone, 6-Diazo-5-

oxo-L-norleucine (DON), Edatrexate, Efaproxiral, Eflornithine, Eniluracil, Erlotinib, Fluorouracil, Gefitinib, Gemcitabine, Goserelin, Histamine, Ifosfamide, Imatinib, Improsulfan, Lanreotide, Leuprolide, Liarozole, Lobaplatin, Cisplatin, Carboplatin, Lonafarnib, Mannomustine, Melphalan, Methotrexate, Methyl Lomustine, Aminolevulinate, Miboplatin, Mitoguazone, Mitoxantrone, Nilutamide, Nimustine, Nolatrexed, Oxaliplatin, Pemetrexed, Phenamet, Piritrexim, Procarbazine, Raltitrexed, Tariquidar, Temozolomide, Thiamiprine, Thioguanine, Tipifarnib, Tirapazamine, 3thiosemicarbazone (3-AP)/3-Aminopyridine-4-Aminopyridine-2-carboxaldehyde methyl-2-carboxaldehyde thiosemicarbazone (3-AMP/Triapine /OCX-191/OCX-0191), Trimetrexate, Uracil Mustard, Uredepa ([Bis(l-aziridinyl)phosphinyl]carbamic acid ethyl ester, ethyl carbamate and Meturedepa.

Both Hydroxy- & Amino- containing (including Amide-NH and Sulphonamide-NH, Carbamate-NH, Sulfamate-NH, and Phosphomide-NH): Ancitabine, Anthramycin, Azacitidine, Bleomycins, Bropirimine, Buserelin, Carubicin, Chlorozotocin, Cladribine, Cytarabine, Daunorubicin, Decitabine, Defosfamide, Docetaxel, Doxorubicin, Ecteinascidins, Epirubicin, Gemcitabine, Hydroxyurea, Idarubicin, Marimastat, 6-Pentostatin, Peplomycin, Perfosfamide, Pirarubicin, Prinomastat, Puromycin, Ranimustine, Streptonigrin, Streptozocin, Tiazofurin, Troxacitabine, Vindesine and Zorubicin.

Carboxyl-containing: Butyric acid.

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ANTIOXIDANTS/FREE RADICAL SCAVENGERS:

Amino-containing (including some investigational drugs): BTX-51072 (4,4-dimethyl-3,4-dihydro-2H-1,2-benzoselenazine), Carnosine, Melatonin, (+)-R-Pramipexole, and Stobadine.

Hydroxyl-containing (including some investigational drugs): Ascorbic acid, Curcumin, Dexanabinol, Edaravon, (-) Epigallocatechin Gallate, Emoxipin, Hydroxytyrosol, Idebenone, Luteolin, Nicanartine, NZ-419, Oxyresveratrol, Probucol (including probucol prodrugs such as AGI-1067 and AGI-1096), Quercetin, Reductic acid, Silybin, Tempol (4-Hydroxy-TEMPO), and alfa-Tocopherol (Vitamin E).

Carboxyl-containing (including some investigational drugs): N-Acetyl L-cysteine, Alfa-Lipoic acid, Raxofelast, and Tetomilast.

Amino-/Hydroxyl-, and Carboxyl-containing (including some investigational drugs): N-Acetyl carnosine, L-Carnitine, and SCMC-Lys (S-carboxymethyl-L-cysteine Lysine salt H₂O).

Amino- and Hydroxyl-containing (including some investigational drugs): BN- 82451, and Zeatin.

BENZODIAZEPINE TRANQUILIZERS AND HYPNOTICS:

Diazepam, Triazolam, Alprazolam, and the like.

ANTIULCER AGENTS:

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Amino-containing (including Amide NH and Sulphonamide NH and Phosphomide NH, etc.): Aldioxa, Benexate HCl, Cimetidine, Ebrotidine, Ecabapide, Esaprazole, Esomeprazole, Famotidine, Irsogladine, Lafutidine, Lansoprazole, Omeprazole, Pantoprazole, Pirenzepine, Polaprezinc, Rabeprazole, Ranitidine, Roxatidine, and Troxipide.

Hydroxyl (and Keto and Keto and/or Carboxyl) -containing: Enprostil, Misoprostol, Ornoprostil, Plaunotol, Rioprostil, Trimoprostil, and Oryzanol A.

Carboxyl-containing: Acetoxolone, Carbenoxolone, Rebamipide, and Sofalcone.

Amino (or Hydroxyl) - and Carboxyl-containing: Cetraxate, Ecabet, S-Methylmethionine, Rosaprostol, and Rotraxate.

Carbonyl-containing: Spizofurone, and Teprenone.

20 ANTICONVULSANTS:

Amino-containing (including Amide NH and Sulphonamide NH Phosphomide NH, etc.): Acetylpheneturide, Albutoin, N-benzyl-3-chloropropionamide, Carbamazepine, Cinromide, Clonazepam, Decimemide, Dimethadione, Doxenitoin, Ethosuximide, Ethotoin, Felbamate, Fosphenytoin, Lamotrigine, Levetiracetam, Mephenytoin, Mephobarbital, Metharbital, Methetoin, Nitrazepam, Oxcarbazepine, Pheneturide, Phenobarbital, Oxicarbamazepine, Phenacemide, Phenetharbital, Phenylmethylbarbituric Acid, Phenytoin, Phethenylate Sodium, Primidone, Progabide, Remacemide, Rufmamide, Suclofenide, Sulthiame, Talampanel, Tetrantoin, Topiramate, Zonisamide, 5-Methyl-5-(3-phenanthryl)hydantoin, and 3-Methyl-5-Valpromide, phenylhydantoin.

Hydroxyl-containing: Ganaxolone.

Hydroxyl-, and Amino-containing (including Amide NH and Sulphonamide NH and Phosphomide NH): 4-Amino-3-hydroxybutyric Acid, Atrolactamide, and Buramate.

Carboxyl- and Amino-Containing (including Amide NH and Sulphonamide NH and Phosphomide NH): Gabapentin, Pregabalin, and Vigabatrin.

Carboxyl-containing: Tiagabine, and Valproic Acid.

ANTIP ARKINSON'S: Levodopa & Carbidopa.

ANTIDEPRESSANT:

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Amino-containing (including Amide NH and Sulphonamide NH and Demexiptiline, Desipramine, Phosphomide NH, etc.): Amoxapine, Caroxazone, Indalpine, Indeloxazine Hydrochloride, Duloxetine, Fluoxetine, Fluvoxamine, Iproclozide, Iproniazid, Isocarboxazid, Levophacetoperane, Maprotiline, Metapramine, Nialamide, Milnacipran, Minaprine, Moclobemide, Nomifensine, Nortriptyline, Octamoxin, Oxypertine, Paroxetine, Protriptyline, Reboxetine, Rolipram, Sertraline, Tofenacin, Tranyleypromine, Viloxazine, Benmoxine, and Rolicyprine.

Hydroxyl-containing: Befloxatone, Bupropion, Fenpentadiol, Hypericin, Opipramol, Pyrisuccideanol, Toloxatone, and Venlafaxine.

Hydroxyl-, and Amino-containing (including Amide NH and Sulphonamide NH and Phosphomide NH): S-Adenosylmethionine, 5-Hydroxytryptophan, and Roxindole.

Carboxyl- and Amino-Containing (including Amide NH and Sulphonamide NH and Phosphomide NH): Amineptine, and Tianeptine.

ANTIHISTAMINIC

Amino-containing (including Amide NH Sulphonamide NH and and Phosphomide NH, etc.): Antazoline, Astemizole, Clobenzepam, Desloratadine, Epinastine, Metron S, Mizolastine, and Tritoqualine.

Hydroxyl-containing: Terfenadine, and N-Hydroxyethylpromethazine Chloride.

Hydroxyl-, and Amino-containing (including Amide NH and Sulphonamide NH and Phosphomide NH, etc.): Cetoxime.

Carboxyl-containing: Acrivastine, Bepotastine, Cetirizine, and Levocabastine, Carboxyl- and Hydroxyl-containing: Fexofenadine.

ANTICANCER, ANTIOXIDATIVE, ANTIINFLAMMATORY, AND CARDIOPROTECTIVE AGENT: Trans-Resveratrol [(E)-3,4',5-trihydroxystilbene).

ANTIDIABETIC: Metformin, andNateglinide/Glipizide/Glibenclamide (Glyburide).

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It should be understood that while the lists of names of various categories of drugs have been included above, such lists are presented in a way of illustration of the structural features of the qualifying drugs in this invention and therefore, the number and types of listed drugs are not necessarily limited thereto. In principal, any amino-, and /or carboxyl, and/or carbonyl-, and/or hydroxyl-containing drug (from both known and investigational drugs), irrespective of its therapeutic category and their mechanism of action, as listed in drug databases such as Merck Index, prous science's ensemble, integrity, iddb, and the like, are generally covered within the true spirit and scope of the present invention. For clarity, in addition to the above lists of drugs, any amino-, and/or carboxyl-, and/or carbonyl-, and/or hydroxyl-containing drug(s) (both known and investigational drugs) from the following therapeutic areas are covered without any limitation:

CENTRAL NERVOUS SYSTEM: Sedatives, Hypnotics, Antidepressants, Antipsychotics and Antimanics, Analgesics & Antipyretics, Antimigraine agents, Anticonvulsants, Drugs used in parkinsonism and movement disorders, Drug for dementia, Antiemtics, drugs for Vertigo, CNS Stimulants & activators.

EYE: Antiinfective eye preparations, Antiinflammatory and antiallergic preparations, antiglucoma drugs and other preparations to cure eye diseases.

EAR, NOSE and OROPHARYNX: Drugs used aural, nasal and oropharyngeal preparation.

CARDIOVASCULAR SYSTEM: Antiarrhythemic drugs, Antihypertensives (including alfa/beta-blockers, channel blockers, ACE inhibitors, Angiotensin II receptor antagonists, diuretics, etc.), Antianginals (includinig nitrates, calcium channel blockers, etc.), Drugs for cardiac failure and shock, Vasodilators, Coagulants, Anticoagulants, Thrombolytics and antiplatelet drugs.

RESPIRATORY SYSTEM: Respiratory stimulants, Antitussives, Expectorants, Mucolytics and Decongestants, Antihistamine agents, and antiasthmatics.

GASTRO INTESTINAL TRACT: Antiulcer and Antisecretory drags (including H₂ receptor antagonists, Proton Pump Iinhibitors, Prostaglandin analogues, etc.),

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Antacids, Antispasmodics and drugs modifying intestinal motility, Antidiarrhoeals (including antimotility and antimicrobial drugs) and drugs acting on gall bladder.

GENITO URINARY SYSTEM: Urinary antiinfectives, Diuretics, Urinary analgesics & antispasmodics, Antiinfective drugs acting on urethra and vagina, drugs acting on uterus, Drugs for prostatic hypertrophy (including alfa blockers and antiandrogens), Drugs for erectile dysfunction, and Spermicidal & nonhormonal contraceptives.

SKIN: Emollients and keratolytics, topical antiinfectives, topical antifungals, topical parasiticidals, topical steroids, topical drugs for acne vulgaris, drugs for psoriasis, pigmentation disorders, and Antiseborrhoeics.

MUSCULO-SKELETAL DISORDERS: Non Steroidal Anti Inflammatory Drugs (NSAIDs) including COX-2 inhibitors, Antiarthritic agents, Immunosuppressants, Topical analgesics, Muscle relaxants and Neuromuscular Drugs.

INFECTIONS AND INFESTATIONS: Penicillin antibiotics, Cephalosporin antibiotics, Quinolone & Fluoroquinolone antibiotics, Macrolide antibiotics, Chloramphenicol, Tetracycline antibiotics, Sulfonamides, Antianaerobics such as Metronidazole, Antitubercular drugs, Antileprosy drugs, Antifungals, Antiprotozoals, Anthelminthics & Antiinfestive Drugs, Antimalarials and Antivirals.

ENDOCRINE SYSTEM: Anabolic and androgenic steroids, Corticosteroids, Oestrogens, Progestogens and Hormonal contraceptives, Fertility Agents, Trophic hormones and related drugs, Thyroid and antithyroid drugs, Antidiabetics and hyperglycaemics.

NUTRITION: Vitamins, Amino acids, Anti-obesity drugs

METABOLISM: Hypolipidaemic drugs (including fibric acid derivatives, statins [(i.e., HMG CoA reductase inhibitors), nicotinic acid group, etc.], Drugs used for Gout and Drugs affecting bone metabolism (including bisphosphonates).

NEOPLASTIC DISORDERS: Anticancer drugs such as alkylating agents, cytotoxic antibiotics, antimetabolites such as cytarbine, Fludarbine, 5-Fluorouracil, Mercaptopurine, Thioguanine, etc., Vinca alkaloids and Etoposide, Taxanes, Topoisomerase 1 inhibitors, Cytotoxic immunosuppressants, Immunostmulants,

Cytoprotectives such as Amifostine, Oestrogens, Progestogens, hormon antagonists and other antineoplastic drugs.

ALLERGY AND IMMUNOLOGY: Antiallurgics such as non-sedative antihistamins (e.g., Cetirizine, Desloratadine, Terfenadine, Fexofenadine, etc.), sedative histamines and histamine receptor blockers.

ANAESTHETICS & SURGICALS: Local anaesthetics, intravenous anaesthetics, inhalation anaesthetics and muscle relaxants.

DRUG COMBINATIONS:

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It is appreciated that NO-releasing prodrugs of any two or more drugs from the above lists of potential drugs can be used in combination depending on the medical application/need. While a combination formulation may occassionally consist of more than two drugs (depending on the medical need), the following pairs of drugs are covered in this invention as illustrative pairs of candidate drugs for combination therapy.

ANTICANCER: Paclitaxel and Doxorubicin, Paclitaxel and Mitomycin C; 9-aminocamptothecin, 3-Arninopyridine-2-carboxaldehyde **Paclitaxel** and thiosemicarbazone (3-AP)/3-Aminopyridine-4-methyl-2-carboxaldehyde thiosemicarbazone (3-AMP) and another known anticancer drug such as Paclitaxel, Doxorubicin, Mitomycin C and the like; CC-1065 and another known anticancer drug such as Paclitaxel, Doxorubicin, Mitomycin C and the like; Trans-Resveratrol [(E)-3,4',5-trihydroxystilbene) and another known anticancer drug such as Paclitaxel, Doxorubicin, Mitomycin C and the like; Retinoic acid (including all trans-retinoic acid) and Butyric acid. Paclitaxel and Captopril, Doxorubicin and Biotin. 5-Fluorouracil and Cytarabine. Edatrexate and Paclitaxel; Cephalosporanic acid and Paclitaxel; Cephalosporin and Paclitaxel; and Paclitaxel and Gemcitabine,

ANTIPERKINSON'S: Levodopa and Carbidopa.

ANTIBIOTICS: Amoxicillin and Clavulanic acid; Ampicillin and Clavulanic acid, Amoxicillin and Pencillinic acid sulfone; Ampicillin and Pencillinic acid sulfone; Olivanic acid (or any carbapenem antibiotic) and a renal dipeptidase (dehydropeptidase I) inhibitor such as 3-substituted Z-2-acylaminopropionic acid and the like.

ANTILIPIDEMIC AND HYPERTENSION: Lifibrol and Lovastatin/Pravastatin/Fluvastatin/Atorvastatin/Simvastatin; Ezetimibe and Lovastatin/Pravastatin/Fluvastatin/Simvastatin;

Amlodipine and Lovastatin/Pravastatin/Fluvastatin/Atorvastatin/Simvastatin.

5 ANTIDIABETIC: Metformin and Nateglinide/Glipizide/Glibenclamide (Glyburide)

ANTIDIABETIC AND HYPERTENSION: Metformin and Lovastatin/Pravastatin/Fluvastatin/Atorvastatin/Simvastatin.

ANTIASTHMATIC, ALLERGIC RHINITIS AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): Pseudoephedrine and Fexofenadine/Cetirizine/Desloratadine/Epinastine; Salbutamol and Ipratropium bromide; Mometasone and Formoterol/Salmeterol; Fluticasone and Formoterol/Salmeterol; Budesonide and Formoterol/Salmeterol.

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ANTIARTHRITIS, INFLAMMATION AND ULCERS: Diclofenac (any known NSAID) and Misoprostol; Diclofenac (any known NSAID) and a proton pump inhibitor such as Omeprazole, Lansoprazol, Rabeprazole, Leminoprazole, Pantoprazole, and the like; A known antibacterial agent and a proton pump inhibitor such as Omeprazole, Lansoprazol, Rabeprazole, Leminoprazole, Pantoprazole, and the like; Naproxen (or any known NSAID) and Prophenazone; Acetaminophen and chlorzoxazone/metaxalone/mephenoxalone.

ANTIVIRAL (HIV/AIDS, PEPATITIS B AND OTHER VIRAL INFECTIONS): Zidovudine and Lamivudine; Triple prodrug of Zidovudine; Lamivudine and Abacavir (Ziagen); Lopinavir and Ritonavir; Lamivudine and Adefovir or its prodrug adefovir dipivoxil; Amprenavir and Zidovudine; Nelfmavir and a nucleoside reverse transcriptase inhibitor such as Zidovudine, Lamivudine, and the like; Stavudine and an antiretroviral agent such as Zidovudine, Lamivudine, and the like; Dideoxyinosine and an antiretroviral agent such as Zidovudine, Lamivudine, and the like; Emtricitabine and Penciclovir/Famciclovir; Acyclovir (or any other known antiviral compound) and a bile acid such as cholate, deoxycholate, chenodeoxycholate, and ursodeoxycholate (for targeting bile acid transporters for enhanced oral bioavailability of the drug; Triple and prodrug of Zidovudine, Lamivudine and Efavirenz.

In addition to the above list of drugs, the the present invention also covers newer drugs with the above mentioned active functional groups as listed in the Merck index (13th edition) and other drug databases such as Prous Science's ensemble, integrity and the investigational drugs as listed in databases such as iddb, ensemble, integrity, and the like without any limitation.

It shoud be understood that either or both of any selected pair of drugs (in any proportion) can be in the form of nitrate ester (NO-releasing) prodrug(s) of formula (I) or pharmaceutically acceptable salts thereof and the other drug can be in its native form. For clarity, let us assume that Ibuprofen and Paracetamol are present as active principles in a pharmaceutical composition. Then, either or both of these drugs can be in their NO-releasing prodrug form (i.e., NO-Paracetamol and Ibuprofen/ Paracetamol and NO-Ibuprofen/ NO-Paracetamol and NO-Ibuprofen, etc.) and they can be present in any proportion.

It should also be understood that a pharmaceutical composition consisting of two or more of the above listed/qualified drugs, one of the drugs can be in the form of NO-releasing (nitrooxy derivative) prodrug and the other drug(s) in the combination can be in the form another type of prodrug(s).

It should also be understood that a pharmaceutical composition containing a combination of one of the above listed/qualified drug(s) and its own prodrug is also covered (i.e., a pharmaceutical composition consisting of NO-Paracetamol and Paracetamol in any proportion). In such pharmaceutical combinations, the free drug will be useful for faster onset of action and the prodrug will be useful for extension of the duration of action as it releases the drug in a controlled fashion over a longer period of time. Such combination drug therapy may also minimize the toxicity and other side effects due to excessive plasma concentration of free drug. It should also be understood that a pharmaceutical combination may contain a prodrug of one of the above listed/qualified drugs and an another type of prodrug of the same drug (i.e., NO prodrug of pracetamol and mutual prodrug of paracetamol with another drug) and these can be present in any therapeutic proportion depending on the medical need.

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EXPERIMENTAL

ABBREVIATIONS USED:

BOP: Benzotriazol-1-yl-oxy-?m(dimethylamino)phosphonium hexafluorophosphate

DMF: N,N-Dimethylformamide

5 DSC: N,N'-Disuccinimidyl carbonate

CDI: N,N'-Carbonyldiimidazole

DTE: Dithioerythritol

DTT: Dithiothreitol

DCC: N,N'-Dicyclohexylcarbodiimide

10 EDAC. HCl: 1-Ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride

HBTU: O-(Benzotriazol- 1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

TBTU: O-(Benzotriazol-l-yl)-N,N,N',N'-tetramethyluroni\ on tetrafluoroborate

EtOH: Ethanol

Et₂O: Diethyl ether

15 THF: Tetrahydrofuran

DMSO: Dimethyl sulfoxide

TEA: Triethylamine

DIPEA: N,N-Diisopropylethylamine

DCM: Dichloromethane

20 EtOAc: Ethyl acetate

DME: Dimethoxyethane

MeOH: Methanol

PE: Petroleum ether

RT: Room temperature

25 TFA: Trifluoroacetic acid

HOBT: N-Hydroxybenzotriazole

SYNTHETIC METHODS:

The prodrugs described herein can be prepared by any number of methods known/obvious to those skilled in the art. The synthetic approaches and the linkages are chosen depending upon the functional groups such as carboxyl, hydroxyl, amino or carbonyl groups present in the drug molecules to be used. The following illustrative

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methods, as shown in Schemes 1 through 9, can be utilized to make carbonate, urethane, amide, ester, N-acyl carbamate, N-acyl amide, N-acyl sulfamate, and N-acyl sulfonamide, N-acyl phosphoramide, N-oxycarbonylsulfonamide, N-oxycarbonylcarbamate linkages, etc., between drug(s) and linker(s).

Methods of making carbonate linkagefs):

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As depicted in the scheme 1, the carbonate linkage between the drug and the linker can be made by reacting the hydroxyl-containing drug (alternatively, hydroxyl group of the linker) with phosgene or its equivalents such as diphosgene, triphosgene, N,N'-carbonyldiimidazole (CDI), N,N'-disuccinimidyl carbonate (DSC), 4-nitrophenyl chloroformate and the like, to give a reactive alkoxycarbonyl derivative, where LG is suitable leaving group such as a halide, imidazole, O-succinimide, 4-nitrophenoxide and the like, which can be reacted with hydroxyl group of the linker (alternatively, hydroxyl group of drug if the linker is converted to active alkoxycarbonyl derivative) in the presence of a suitable base and solvent.

Rx and Ry are any monovalent organic radicals;

Scheme 1

Bases such as triethylamine, diisopropylethylamine, 4-(dimethylamino)pyridine (DMAP), and the like, can be used. Suitable solvents include CH₂Cl₂, CHCl₃, DMF, THF, ACN, ethyl acetate, ethyl ether and the like.

Method(s) of making urethane linkage(s):

As shown in scheme 2, the urethane linkage between the drug and the linker can be made by reacting the hydroxyl-containing linker with phosgene or its equivalents (defined above) to give a reactive alkoxycarbonyl derivative, which can be reacted with amino-containing drug in the presence of a suitable base and solvent. Alternatively, a urethane linkage can be made by adding an alcohol to an isocyanate.

Scheme 2

Suitable bases and solvents are same as defined above.

Methodfs) of making amide or ester linkagefs):

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As shown in the Scheme 3, an amide or ester linkage between the drug and the linker can be made by reacting a carboxyl-containing drug with an amino- or hydroxylcontaining linker in the presence of a suitable coupling agent, base and solvent. Alternatively, the carboxyl-containing compound can be first converted to reactive carbonyl derivative such as an acid halide, a succinimide ester, a pentafluorophenyl ester, an imidazolide and the like, which can be treated with amino-containing or hydroxylcontaining linker in the presence of a suitable base and solvent to afford the corresponding amide or ester linkage(s), respectively (see, Bodanszky, M. and Bodanszky, A., The Practice of Peptide Synthesis, Springer-Verlag, New York, 1984)

Rx, Ry, and Rz are any monovalent organic radicals;

Scheme 3

Suitable coupling agents include DCC, EDCLHCI, BOP, HBTU, TBTU, DCC/HOBT, EDC/HOBT, and the like. Suitable bases and solvents are same as defined above.

Method(s) of making N-acyl carbamate and N-acyl urea linkage:

The linkage such as N-acyl carbamate linkage between the linker and drug can be made as shown in Scheme 4. Thus, treatment of an alcohol with phosgene or its

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equivalent can yield the corresponding carbonochloridate, which upon treatment with ammonia gas can give the corresponding carbamate intermediate. The carbamate nitrogen can be acylated by a suitable carboxylic acid derivatives such as anhydride or acid halide, a succinimide ester, a pentafluorophenyl ester, an imidazolide, and the like, in the presence of a suitable base to yield the corresponding N-acyl carbamate. Alternatively, N-acyl carbamate can be made by the reaction of an alcohol with N-acyl isocyanate, which can be prepared either by the reaction of the corresponding amide with oxalyl chloride (See, Speziale, A. J. et al., J. Org. Chem. 1962, 27, 3142; Speziale, A. J. et al., J. Org. Chem. 1963, 28, 1805-1811) or by the reaction of the corresponding acid chloride with silver cyanate. (See, Hill, AJ. et. al., J. Am. Chem. Soc, 1940, 62, 1595; Kim, D.K. J. Heterocyclic Chem. 1995, 32, 1625).

Rx, Ry and Rz are any monovalent organic radicals.

Scheme 4

Suitable bases and solvents are same as defined above.

Method(s) of making N-acyl amide linkage:

The N-acyl amide linkage between the linker and drug can be made as shown in Scheme 5. Thus, the amide nitrogen can be acylated by a suitable carboxylic acid derivatives such as anhydride or acid halide, a succinimide ester, a pentafluorophenyl ester, an imidazolide, and the like, in the presence of a suitable base to yield the corresponding N-acyl amide.

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Rx and Ry are any monovalent organic radicals.

Scheme 5

Suitable bases and solvents are same as defined above.

Methodfs) of making N-acyl sulfamate linkage:

The linkage such as N-acyl sulfamate between the linker and drug can be made as shown in Scheme 6. Thus, treatment of an alcohol with sulfuryl chloride in the presence of suitable base gives the intermediate sulfochloridate, which can be converted to the corresponding sulfamate. Acylation of sulfamate nitrogen with a suitable carboxylic acid derivatives such as anhydride or acid halide, a succinimide ester, a pentafluorophenyl ester, an imidazolide, and the like, can yield the corresponding N-acyl sulfamate.

Rx and Ry are any monovalent organic radicals.

Scheme 6

Suitable bases and solvents are same as defined above.

MethodCs) of making N-acyl/oxycarbonyl sulfonamide linkages:

The N-acyl/oxycarbonyl sulfonamide linkage between the linker and drug can be made as shown in Scheme 7. Thus, a sulfonamide nitrogen can be acylated by a suitable carboxylic acid derivatives such as anhydride or acid halide, a succinimide ester, a pentafluorophenyl ester, an imidazolide, and the like, to yield the corresponding N-acylsulfonamide, which can me metallated using an inorganic base. Similarly, the

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sulfonamide nitrogen can be acylated by a suitable formyl chloride derivative such as alkyloxycarbonyl chloride, imidazolide and the like, to yield the corresponding N-alkyloxycarbonyl sulfonamide as shown in the scheme. Alternatively, the same linkage can be made by the reaction of an alcohol with sulfonyl isocyanate which can be prepared by known methods such by treatment of sulfonamide with oxalyl chloride (see, Hans Krzikalla et al., US2666787 or Smith, J. et al., J. Org. Chem. 1965, 30, 1260-1262) or by treatment of sulfonyl chloride with silver cyanate (See, Smith, J. et al., J. Org. Chem. 1965, 30, 1260-1262).

Rx, and Ry are any monovalent organic radicals; M is a metal ion; x is 1-4 Scheme 7

Suitable bases and solvents are same as defined above.

Method(s) of making N-oxycarbonylcarbamate and N-oxycarbonylurea linkages:

The N-oxycarbonylcarbamate (or N-oxycarbonylurea) linkage between the linker and drug can be made as shown in Scheme 8. Thus, carbamate nitrogen can be acylated by suitable formyl chloride derivatives such as alkyloxycarbonyl chloride,

imidazolide and the like, to yield the corresponding N-alkyloxycarbonylcarbamate scheme. Nthe Alternatively, the N-oxycarbonylcarbamate shown in oxycarbonylurea) linkage between the linker and drug can be made by the reaction of an alcohol (or an amine) with carbamoyl isocyanate (IP15A), which can be prepared by known methods such by treatment of carbamate with oxalyl chloride (See, Grehn L, et al, Synthesis, 1988, 922-994) or by treatment of a formyl chloride with silver cyanate (See, Kim, D.K. et al., J. Heterocyclic Chem. 1995, 32, 1625). Alternatively, Noxycarbonylcarbamate (or N-oxycarbonylurea) can be prepared in two steps. Step 1: reaction of an alcohol or phenol with chlorocarbonyl isocyanate to give N-oxycarbonyl carbamoyl chloride intermediate (IP15B). Step 2: reaction of the intermediate IP15B with the same or another alcohol or phenol or an amine. (For a review on chemistry of chlorocarbonyl isocyanate, see, Gorbatenko, V. I. Tetrahedron, 1993, 49, 3227).

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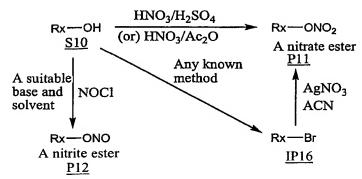
Rx, Ry and Rz are any monovalent organic radicals.

Scheme 8

Suitable bases and solvents are same as defined above.

Method(s) of making Nitrate CnitrooXyl or Nitrite (nitrosyloxy) esters:

The nitrate or nitrite esters can be made as shown in Scheme 9. Thus, a nitrate or nitrite ester can be made by treating an alcohol with HNO₃/H₂SO₄ (or HNU₃/Ac₂O) or nitrosyl chloride, respectively. Alternatively, a nitrate ester can be made by treating a halide (bromide or iodide is preferred) with silver nitrate in a polar aprotic solvent such as acetonitrile.



Rx is any monovalent organic redical.

Scheme 9

Compounds (Prodrugs) of the formula (I) containing bio-cleavable linkers and linkages can be synthesized by various methods obvious to those skilled in the art. As a matter of illustration, any of the approaches shown in the following schemes can be used to make such prodrugs of the formula (I) described herein.

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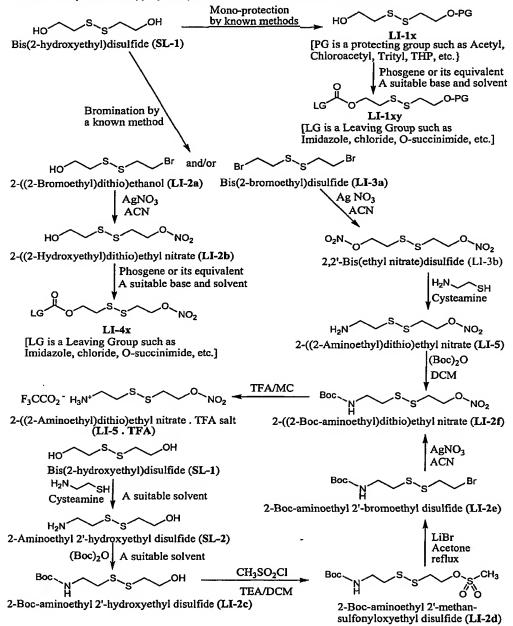
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Monoprotection of diol or aminoalcohol or diamino compounds [i.e., linker(s)] with suitable protecting groups and their selective removal at appropriate stage of the synthesis are carried out as described in Theodora W. Greene and Peter G.M. Wuts, "Protective Groups in Organic Synthesis", 3rd edition, John Wiley and Sons, Inc. New York (1999), the disclosures of which are incorporated herein by reference. Suitable protecting groups (PGs) include, but not limited to, acetyl, Boc, Fmoc, benzoyl, pivaloyl, trityl, tetrahydropyranyl (THP), and silyl (TBDMS, TMS, etc.). Obviously, selection of a suitable protecting group is very crucial for the success of a chosen method for the synthesis of prodrugs described in this invention.

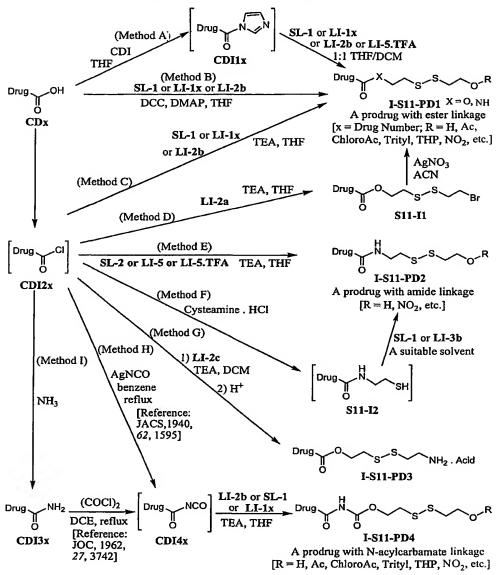
Synthesis of appropriately derivatized/modified bio-labile linker is shown in Scheme 10.

Scheme 10: Synthesis of appropriately derivatized/modified linker intermediates

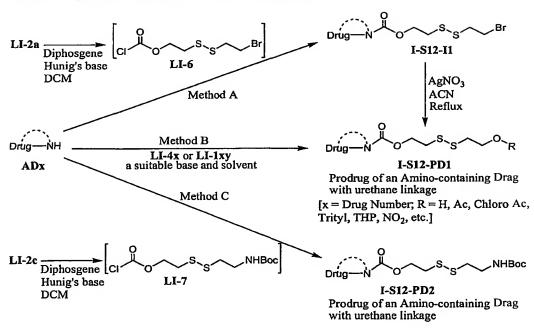


Some of the methods for the synthesis of prodrugs (including NO-releasing prodrugs) of carboxyl-, amino-, and hydroxyl-containing drugs are shown in Schemes 11 through 14.

Scheme 11: Synthesis of Prodrugs of Carboxyl-containing Drugs



Scheme 12: Synthesis of Prodrugs of Amino-containing Drags



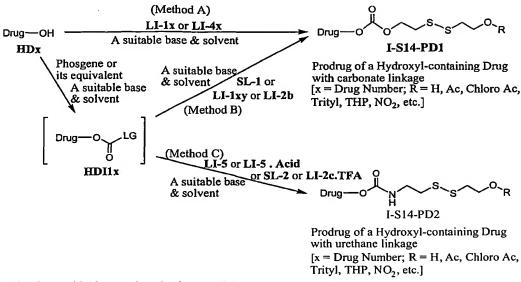
Scheme 13: Synthesis of Prodrugs of Amide/Sulfonamide-containing Drugs:

Prodrug of an Amide/Sulfonamide-containing Drug with N-oxycarbonylamide/sulfonamide linkage

AMDx is a $CONH_2$ -containing drugs such as vapromide, levotiracetam, carbamazepine, and the like. SAMDx is a SO_2NH_2 -containing drugs such as valdecoxib, celecoxib, and the like.

Scheme 14: Synthesis of Prodrugs of Hydroxyl-containing Drugs

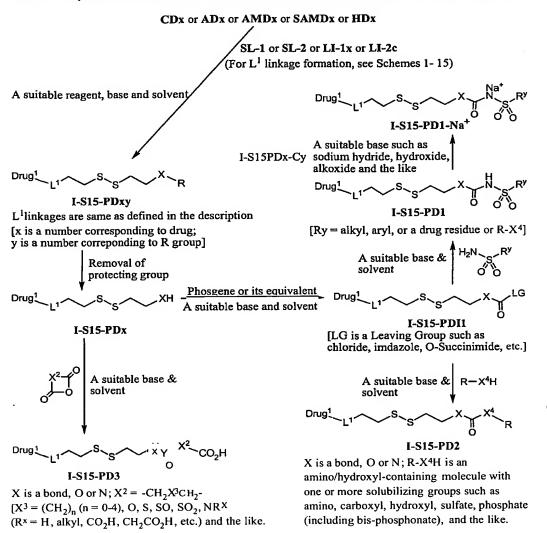
A) Prodrugs with carbonate and carbamate linkages:



B) Prodrugs with N-oxycarbonylcarbamate linkage:

Some of the methods for the synthesis of prodrugs (including NO-releasing prodrugs and water-soluble prodrugs) are shown in Schemes 15 and 16.

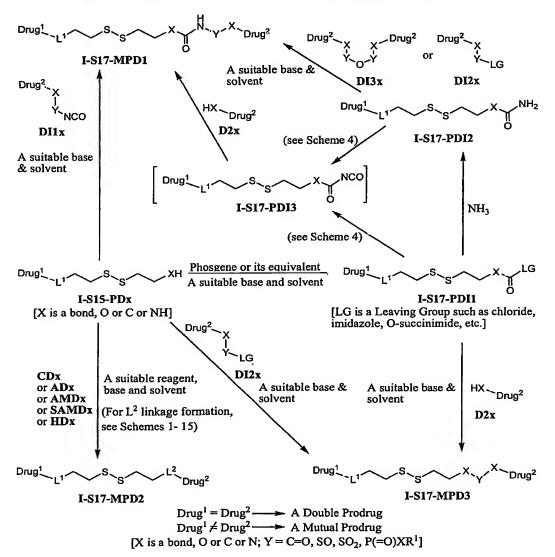
Scheme 15: Synthesis of Water-soluble Prodrug(s) using a bio-cleavable linker(s) and spacer linker (s)



Scheme 16: Synthesis of Prodrugs containing a biocleavable linker and various types linkages

Double/Mutual prodrugs described in this invention can be synthesized by any of the approaches depicted in Schemes 17 through 19.

Scheme 17: Synthesis of Mutual Prodrug(s) using a bio-cleavable linker(s) and spacer linker (s)



Scheme 18: Synthesis of Double/Mutual Prodrug(s) with additional linkers

Scheme 19: Synthesis of Mutual Prodrag(s) using modified bio-cleavable linker(s)

Scheme 20: Synthesis of Mutual Prodrag(s) using modified bio-cleavable linker(s)

As a matter of illustration, mutual prodrug of desloratadine and pseudoephidrine was synthesized as depicted in Scheme 21.

Scheme 21: A Mutual Prodrug of Desloratadine and Pseudoephedrine

Scheme 22: Synthesis of a water-soluble prodrug of paclitaxel

Scheme 23: Generation of Paclitaxel from a Prodrug of Isotaxel

Y = O, NR¹ (R¹ = H, Alkyl, Aralkyl, Cycloalkyl), (CH₂)_nC(=O) (n=l-6), (CH₂)_nCO;f Z = C=O, SO₂, P(=O)YR³ (R³ = H or a metal ion)

 $R^2 = H$, a bond, $CH_2CH_2N(CH_3)_2$. HCl, an Amino acid, or any molecule containing solubilizing groups such as carboxylic acid, sulphonic acid, hydroxyl, amino groups, polyethyleneglycol (PEG), a metal ion such a Na^+ , Ca^{2+} , etc.

Scheme 24: An alternative method for the synthesis of Linker Intermediates LI-2b and LI-5

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Synthesis of 2-[(2-hydroxyethyl)dithio]ethyl acetate (LI-Ia):

Acetic anhydride (5.67 ml, 56.87 mmol) and pyridine (40.4 ml, 499 mmol) were added to a solution of 2-(hydroxyethyl)disulfide (SL-I, 15.39 g, 99.78 mmol) in DCM (350 mL) at RT and the mixture was stirred at RT for 16 h. The mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, afforded 8.16 g (42%) of **LI-Ia** as a pale yellow oil. 1 H-NMR (300 MHz, CDCl₃): δ 2.00 (bs, IH), 2.08(s, 3H), 2.80-2.95 (m, 4H), 3.89 (t, 2H, J = 6 Hz), 4.35 (t, 2H, J = 6 Hz), MS: (m/z) 219 [M]⁺.

Example 2

Synthesis of 2-{[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]dithio} ethanol (LI-Ib):

This compound was synthesized by a method described by K. F. Bernady *et al.*, *J. Org. Chem.*, 1979, 44, 1438. Dihydropyran (8.41 g, 100 mmol) was added to a solution of SL-1 (15.4 g, 100 mmol) in DCM (200 mL) at 0-5 $^{\circ}$ C, followed by PTSA (-5%) and stirred at RT for 5 h. The mixture, after usual aqueous work-up and chromatographic purification, afforded 14.5 g (50%) of **LI-1b.** 1 H-NMR (300 MHz, CDCl₃): δ 1.5-1.9 (m, 6H), 2.88 (t, 2H, J = 6 Hz), 2.94 (t, 2H, J - 6 Hz), 3.45-3.57 (m, IH), 3.67-3.78 (m,IH), 3.85-4.05 (m, 2H), 3.90 (t, 2H, J = 6 Hz), 4.65 (s, IH).

20 Example 3

Synthesis of 2-{[2-(Trityloxy)ethyl]dithio}ethanol (LI-Ic):

This compound was synthesized by a method described by O. Hernandez *et al*, *Tetrahedron Letters*, **1981**, *22*, 1491-1494. Thus, 8.58 g (21.4 mmol) of 4-dimethylamino-N-triphenylmethylpyridinium chloride (A.V. Bhatia et al., *Organic Synthesis*, 1997, 75, 184-185) was added to a solution of **SL-I** (3.0 g, 19.45 mmol) in DCM (90 mL) and stirred at RT for 24 h. The mixture, after usual aqueous work-up and chromatographic purification, afforded 2.86 g (37%) of **LI-Ic.** ¹H-NMR (300 MHz, CDCl₃): δ 2.70 (t, 2H, J = 6.0 Hz), 2.88 (t, 2H, J = 6.0 Hz), 3.39 (t, 2H, J = 6.0 Hz), 3.80 (q, 2H, J = 6.0 Hz), 7.24-7.33 (m, 10H), 7.44-7.46 (m, 5H). MS (m/z): 396 [M]⁺.

Example 4

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10 Synthesis of chloroacetic acid 2-(2-hydroxyethyldisulfanyl)ethyl ester (LI-Id):

To a solution of SL-I (23 g, 150 mmol) in DCM (250 mL) at 0 °C were added TEA (10.12 g, 100 mmol) and chloroacetyl chloride (11.3 g, 100 mmol) and stirred overnight at RT. The reaction mixture was concentrated and purified by column chromatography to afford 8.3 g (37%) of LI-Id. ¹H-NMR (300 MHz, CDCl₃): δ 2.88 (t, 2H, J = 5.7 Hz), 2.95 (t, 2H, J = 6.6 Hz), 3.89 (t, 2H, J = 5.7 Hz), 4.09 (s, 2H), 4.47 (t, 2H, J = 6.6 Hz).

Example 5

Synthesis of 2-((2-hydroxyethyl)dithio)ethyl nitrate (LI-2b) and 2,2'-bis(ethyl nitrate)disulfide (LI-3b):

These intermediates were synthesized in two steps as shown in Scheme 10.

- 20 Step 1: Synthesis of 2-((2-bromoethyl)dithio)ethanol (LI-2a) and bis(2-bromoethyl)disulfide (LI-3a): These compounds can be synthesized *via* bromination of SL-I by a known bromination method. (For a suitable bromination method, see Fruniss, B.S. *et al.*, Vogel's Text Book of Practical Organic Chemistry, 5th edition, Pearson Education, Singapore, 1989; pp 559-579). The following methods were explored:
- Method 1: To a solution of SL-I (15g, 97.4 mmol) in DMF (50 mL) was added PPh₃ (25.5g, 97.4 mmol) and cooled to 0 °C. Bromine (3.33 mL, 64.9 mmol) was added dropwise and stirred at RT for 18 h. TLC of the mixture showed the mono-bromo derivative LI-2a as the major product with only trace amounts of dibromide LI-3a. The mixture was diluted with water and extracted with EtOAc. After usual aqueous work-up and chromatographic purification, 3.65 g (26%) of LI-2a were obtained. ¹H-NMR (300 MHz,

CDCl₃): δ 1.82 (s, IH), 2.88 (t, 2H, J = 5.8 Hz), 3.08 (t, 2H, J = 7.90 H), 3.63 (t, 2H, J = 7.90 Hz), 3.90 (t, 2H, J = 5.8 Hz).

Method 2: To a solution of SL-I (40 g, 0.26 mol) in DCM (400 mL) at 0 °C was added a solution of PBr₃ (24.62 mL, 0.26 mol) in DCM (50 mL) and the mixture was stirred at RT for 15 h. TLC indicated formation of LI-3a as the major product with trace amounts of LI-2a. The reaction was quenched by the addition of water and extracted with DCM. After usual aqueous work-up and chromatographic purification, 33 g (45.3%) of LI-3a were obtained. ¹H-NMR (500 MHz, CDCl₃): δ 3.1-3.15 (m, 4H), 3.60-3.66 (m, 4H). MS (Cl)+ m/z: 277.69 [M+H]+, 279.66. An alternative synthesis of LI-3a has been reported.

10 (Sharma, M. et al, Bioorg. Med. Chem. Lett., 2004, 14, 5347-5350).

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Method 3: To a cold suspension of SL-I (20 g, 129 mmol) in DCM (400 mL) was added CBr₄ (42 g, 129 mmol) and stirred for 10 min. PPh₃ (34 g, 129 mmol) was then added and stirred at RT for 14 h. The reaction mixture was concentrated and the residue purified by column chromatography to give 13.5 g (52.3%) of **LI-2a** and 13.0 g (36%) of **LI-3a**.

15 These compounds were identical (by TLC, NMR and MS) to those obtained in Methods 1 and 2 described above.

Synthesis of 2-((2-hydroxyethyl)dithio)ethyl nitrate (**LI-2b**): To a solution of **LI-2a** (2g, 9.21 mmol) in acetonitrile (15 mL) was added AgNO₃ (1.88g, 11.05 mmol) portion-wise and the mixture was stirred at RT in the dark for 45 min. The reaction mixture was filtered through celite and the filtrate was concentrated. The residue, after usual aqueous work-up and chromatographic purification gave 1.46 g (74%) crude **LI-2b** which was used for the next reaction without further purification. An analytical sample was obtained by chromatographic purification. 1 H-NMR (300 MHz, CDCl₃): δ 2.89 (t, 2H, J = 6.0 Hz), 2.98 (t, 2H, J = 7.5 Hz), 3.90 (t, 2H, J = 6.0 Hz), 4.74 (t, 2H, J = 7.5 Hz); MS (EI)⁺ (m/z): 199 [M]⁺.

Synthesis of 2,2'-bis(ethyl nitrate)disulfide (LI-3b): AgNO₃ (8.01 g, 47.12 mmol) was added portion-wise to a solution of LI-3a (6.0 g, 21.42 mmol) in acetonitrile (40 mL) at RT in the dark and stirred for 30 min. The mixture was filtered through celite and the filtrate was concentrated *in vacuo* at 35 °C to afford 4.6 g (88%) of LI-3b, which was used without further purification. An analytical sample was obtained by chromatographic

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purification (3-15% EtOAc in petroleum ether). 1 H-NMR (300 MHz, CDCl₃): δ 3.10 (t, 4H, J = 6.7 Hz), 4.71 (t, 4H, J = 6.7 Hz). MS (EI)⁺m/z: 244 [M]⁺.

Example 6

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Synthesis of tert-butyl 2-[(2-hydroxyethyl)dithio]ethylcarbamate (L1-2c): To a solution of cysteamine hydrochloride (15 g, 132 mmol) in MeOH (130 mL) at 0-5 °C was added TEA (37 mL, 264 mmol), followed by a solution of SL-I (20.4 g, 132 mmol) in DCM (50 mL) and stirred at RT for 6 h. The mixture, which contained the intermediate SL-2, was cooled and (Boc)₂O (63.4 g, 290.4 mmol) was added and stirred overnight. MeOH was removed under vacuum. After usual aqueous work-up and chromatographic purification, L1-2c was obtained as a colorless oil (14.6 g, 44%).

The above linker intermediate can also be prepared by the following method: Step 1: TEA (37 ml, 264 mmol) and a solution of $(Boc)_2O$ (48 g, 220 mmol) in DCM (100 mL) were added to a suspension of cystamine dihydrochloride (20 g, 88.8 mmol) in of DCM (300 mL) and stirred at RT for 15 h. The mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, gave 30 g (96%) of tert-butyl 2-($\{2-[(tet-butoxycarbonyl)amino]ethyl\}dithio)ethylcarbamate as a white solid. <math>^{1}H$ -NMR (300 MHz, CDCl₃): δ 1.43 (s, 18H), 2.78 (t, 4H, J = 6.3Hz), 3.44 (q, 4H, J = 6.0 Hz), 5.00 (bs,lH). MS (m/z): 353.18 [M+H]+, 375.24 [M+Na]+.

Step 2: A solution of 2-mercaptoethanol (1.44 g, 18.5 mmol) in DCM (10 mL) was added to a mixture of tert-butyl 2-({2-[(tert-butoxycarbonyl)amino]ethyl}dithio)ethyl carbamate (5.0 g, 14.2 mmol) and TEA (3.87 ml, 27.7 mmol) in DCM (30 mL) and stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 2.0 g (56%) of **LI-2c** was obtained. 1 H-NMR (300MHz, CDCl₃): δ 1.43 (s, 9H), 2.79 (t, 2H, J = 6.5Hz), 2.87 (t, 2H, J = 5.7Hz), 3.48 (q, 2H, J = 6Hz), 3.88 (t, 2H, J = 5.5 Hz), 4.8 (bs,lH). MS (m/z): 254 [M+H]+, 276.13 [M+Na]+.

Removal of the Boc group of LI-2c was accomplished as described in Example 10 to afford the TFA salt, LI-2c.TFA.

Obviously, the linker intermediates LI-2b and LI-2c can also be synthesized by following the method outlined in Scheme 24.

Synthesis of 2-Boc-aminoethyl-2'-methansulfonyloxyethyl disulfide (LI-2d): To an ice-cold solution of LI-2c (9 g, 35.52 mmol) in DCM (80 mL) and TEA (9.9 mL, 71.04 mmol) was added methanesulfonyl chloride (4.2 mL, 53.28 mmol). The reaction mixture was stirred at 0-5 0 C for 45 min, then diluted with DCM. After usual aqueous work-up and chromatographic purification, 13.38 g of LI-2d were obtained, which was pure enough for further use. 1 H-NMR (300 MHz, CDCl₃): δ 1.43 (s, 9H), 2.80 (t, 2H, J = 6.4 Hz), 2.98 (t, 2H, 5.7 Hz), 3.05 (s, 3H), 3.35-3.45 (m, 2H), 4.45 (t, 2H, J = 6.7 Hz), 4.78 (br s, 1H).

10 Example 8

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Synthesis of 2-Boc-aminoethyl-2'-bromoethyl disulfide (LI-2e): To a solution of LI-2d (13 g, 39.27 mmol) in acetone (100 mL) at RT was added LiBr (6.82 g, 78.54 mmol) and stirred under reflux for 1 h. The reaction mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, afforded 8.8 g (78%) of LI-2e. 1 H-NMR (300 MHz, CDCl₃): δ 1.44 (s, 9H), 2.80 (t, 2H, J = 6.32 Hz), 3.06 (t, 2H, J = 6.73 Hz), 3.44 (q, 2H), 3.61 (t, 2H, J = 7.62 Hz), 4.87 (br s, IH). MS (EI)⁺ m/z: 317 [M+H]⁺.

Example 9

Synthesis of 2-((2-Boc-aminoethyl)dithio)ethyl nitrate (LI-2f): To a solution of **LI-2e** (8 g, 25.3 mmol) in acetonitrile (80 mL) was added AgNO₃ (5.16 g, 30.36 mmol) portionwise and stirred at RT for 1 h in the dark. The mixture was filtered through celite and the filtrate was concentrated. The residue obtained was purified by column chromatography to afford 6.34 g (84%) of **LI-2f.** ¹H-NMR (300 MHz, CDCl₃): δ 1.44 (s, 9H), 2.80 (t, 2H, J = 6.32 Hz), 3.06 (t, 2H, J = 6.73 Hz), 3.44 (q, 2H), 4.70 (t, 2H, J = 7.62 Hz), 4.87 (br s, IH). MS (EI)⁺ m/z: 299 [M+H]⁺.

The above linker intermediate was also prepared by the following method: TEA (3.56 g, 35.2 mmol) was added to a solution of cysteamine hydrochloride (2g, 17.60 mmol) and LI-3b (4.29g, 17.6mmol) in methanol (25mL) at 0 °C and stirred at RT for 4 h. To the mixture, which contained the intermediate free amine (LI-5), a solution of (BoC)₂O (7.68 g, 35.2 mmol) and TEA (3.56 g, 35.2 mmol) in MeOH (10mL) was added and the mixture was stirred overnight. The reaction mixture was filtered through celite

and evaporated to dryness. The residue was purified by column chromatography to afford 0.380 g (7 %) of LI-2f.

Example 10

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Synthesis of 2-((2-Aminoethyl)dithio)ethyl nitrate.TFA salt (LI-5.TFA): To an ice-cold solution of LI-2f (2 g, 6.7 mmol) in DCM (20 mL) was added TFA (5 mL) and stirred at room temperature for 1 h. The mixture was concentrated, the residue was triturated with ether and concentrated to remove traces of TFA and finally dried to afford LI-5.TFA, which was used as such in further reactions.

The above linker intermediate **LI-5.TFA** was also synthesized as described below: TEA (3.56 g, 35.2mmol) was added drop-wise to a solution of cysteamine hydrochloride (2g, 17.60mmol) and **LI-3b** (4.29g, 17.6mmol) in MeOH (25mL) at 0 °C and stirred at RT for 4 h. The mixture was cooled to 0 °C and a solution of (Boc)₂O (7.68 g, 35.2mmol) in MeOH (10 mL) was added, followed by TEA (3.56 g, 35.2mmol), and stirred overnight at RT. The reaction mixture was filtered through celite and the filtrate concentrated. The residue was purified by column chromatography to afford 0.38 g (7.25%) of LI-2f, which was identical (TLC and ¹H-NMR) to that obtained in Example 9. Removal of the Boc group from **LI-2f** to give **LI-5.TFA** was accomplished as described in Example 10.

Example 11

Synthesis of methyl r(2-hvdroxyethyl)dithiolacetate (L3I2a): Methyl mercaptoacetate (10.32 g, 97.4 mmol) was added to a solution of SL-I (10.0 g, 64.93 mmol) in DCM (150 mL) at RT, followed by TEA (18 mL, 129 mmol) and the mixture was stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 2.7 g (22.9 %) of L3I2a were obtained. ¹H-NMR (300 MHz, CDCI₃): δ 2.95 (t, 2H, J = 2.5 Hz), 3.49 (s, 2H), 3.76 (s, 3H), 3.86 (q, 2H, J = 5.64). MS (m/z): 182 [M+H]⁺.

Example 12

Synthesis of prodrug I-C1-PD10: This prodrug was synthesized as described in Scheme 11, Method B. Thus, TEA (0.73 mL, 10 mmol) was added to a suspension of cetirizine dihydrochloride (2.0 g, 4.68 mmol) in DCM (50 mL), followed by a solution of SL-I (0.72 g, 4.67 mmol), DCC (1.13 g, 5.47 mmol) and DMAP (0.112g, 1 mmol) and stirred at RT for 15 h. The mixture was concentrated and the residue, after usual aqueous work-

up and chromatographic purification, gave 0.44 g (19%) of **I-C1-PD10.** ¹H-NMR (300 MHz, CDCl₃): δ 2.50 (bs, 4H), 2.80 (bs, 6H), 2.87 (t, 2H, J = 6.09 Hz), 2.94 (t, 2H, J = 7.32 Hz), 3.75 (m, 2H), 3.86 (t, 2H, J = 6.12 Hz), 4.13 (s, 2H), 4.24 (s, IH), 4.40 (t, 2H, J = 6.09 Hz) and 7.22-7.35 (m, 9H). MS (m/z): 527 [M+H]⁺.

5 Example 13

Synthesis of prodrug I-C1-PD6: Step 1: To a suspension of aspirin (3 g, 16.65 mmol) in benzene (25 mL) and DMF (2 drops) at 0-5 ⁰C was added oxalyl chloride (1.7 mL, 19.98 mmol) in benzene (5 mL). The reaction mixture was refluxed at 85 ⁰C for 2 h, cooled to RTe and concentrated to give a yellow oil.

- 10 Step 2: The yellow oil was dissolved in benzene (30 mL), silver cyanate (2.99 g, 19.98 mmol) was added and the mixture was refluxed for Ih in the dark.
 - Step 3: The reaction mixture was cooled to RT, and a solution of SL-I (2.56 g, 16.65 mmol) in benzene (5 mL). The reaction mixture was stirred for Ih, filtered through celite, concentrated and purified by column chromatography to afford 2.24 g (54%) of I-Cl-
- PD6. ¹H NMR (CDCl₃, 300 MHz): δ 2.12 (s, 3H), 2.83-2.91 (m, 4H), 3.84 (t, J = 5.9 Hz, 2H), 4.27 (t, J = 5.16 Hz, 2H), 6.20 (br s, IH), 7.06 (d, J = 8.21 Hz, IH), 7.19 (t, J = 7.55 Hz, IH)₅ 7.59 (t, J = 7.24 Hz, IH), 7.97 (d, J = 6.82 Hz, IH). MS: m/z 360.06 [M+H]⁺, 377.05 [M+NH₄]⁺, 382.01 [M+Naf, 357.96 [M-H]⁻.

Example 14

Synthesis of prodrug I-Cl-PDll:To a solution of SL-I (7g, 45.45 mmol) and valproic acid (7.85 g, 54.5 mmol) in DCM (80 mL) was added DCC (11.26 g, 54.5 mmol), followed by DMAP (6.65 g, 54.5 mmol), and the resulting suspension was stirred at RT for 18 h. After usual aqueous work-up and chromatographic purification, 2.82 g (22 %) of I-C1-PD11 were obtained as a colorless oil. ¹H NMR (CDCl₃, 300 MHz): δ 0.86-0.93
(m, 6H), 1.22-1.29 (m, 8H), 1.32-1.59 (m,4H), 2.37 (m,lH), 3.89 (t, 2H, J = 5.7 Hz), 4.35(t, 2H, J = 6.5 Hz).

Example 15

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Synthesis of prodrug I-C1-PD13: To a solution of valpromide (5 g, 34.9 mmol) in DCE (50 mL) was added oxalyl chloride (3.7 mL, 41.88 mmol) at 0 °C and refluxed for 16 h. The mixture was added to a solution of SL-I (10.76 g, 69.8 mmol) in DCE (80 mL) and stirred overnight at RT. After usual aqueous work-up and chromatographic purification,

5.01 **g** (44%) of I-C1-PD13 were obtained as a colorless oil. ¹H NMR (CDCl₃, 300 MHz): δ 0.89 (t, 6H, J = 7.21 Hz), 1.23-1.66 (m, 9H), 2.90 (t, 2H, 5.82 Hz), 2.97 (t, 2H, J= 6.46Hz), 3.90 (t, 2H, J= 5.82Hz), 4.44 (t, 2H, J= 6.48 Hz), 7.61 (br s, IH)

Example 16

Synthesis of prodrug I-C1-PD14: To a cold solution of diphosgene (0.9 mL, 7.14 mmol) in DCM (5 mL) was added a solution of I-C1-PD11 (1 g, 3.57 mmol) and DIPEA (1.9 mL, 10.71 mmol) in DCM (5 mL). The reaction mixture was stirred at RT for 30 min. DCM and excess phosgene were removed under vacuum and the resulting solid was dissolved in DCM (5 mL). To it was added a suspension of methanesulfonamide (0.41 g, 4.284 mmol) and DIPEA (1.9 mL, 10.71 mmol) in DCM (5 mL) at 0-5 °C and the mixture was stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 1.1 g (77%) of I-C1-PD14 were obtained as a white solid. ¹H NMR (CDC1₃, 300 MHz): δ 0.89 (t, 6H, J = 7.22 Hz), 1.27-1.63 (m, 8H), 2.34-2.43 (m, 1H), 2.90 (t, 2H, J = 7.0 Hz), 2.96 (t, 2H, J = 6.13 Hz), 3.30 (s, 3H), 4.36 (t, 2H, J = 6.98 Hz), 4.45 (t, 2H, J = 6.14 Hz). MS: (ES+) m/z 402 [M+H]+, 419 [M+NH₄]+, 424 [M+Na]+, 440 [M+K]+; (ES-) 401 [M-H]-.

Example 17

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Synthesis of prodrug I-A1-PD1:

This prodrug was synthesized as shown in Scheme 14, Method B. Thus, to a solution of amlodipine (18.75 g, 45.86 mmol) in DCM (100 mL) at 0 $^{\circ}$ C was added triphosgene (4.62 g, 15.59 mmol) followed by TEA (7.71 g, 76.35 mmol) in DCM (10 mL) and stirred at RT for 3 h. To this was added a solution of **LI-Ia** (9.0 g, 48.86 mmol) and TEA (4.63 g, 45.86 mmol) in DCM (10 mL) at 0 $^{\circ}$ C and stirred at RT for 3 d. The mixture was concentrated and the residue purified by column chromatography to yield 23 g (79.5%) of **I-AI-PDI**. 1 H-NMR (300 MHz, CDCl₃): δ 1.16 (t, 3H, J = 7.5 Hz), 2.05 (s, 3H), 2.34 (s, 3H), 2.86-2.94 (m, 4H), 3.43-3.45 (m, 2H), 3.59-3.62 (m, 5H), 4.0-4.35 (m, 4H), 4.30-4.35 (m, 4H), 4.69 (q, 2H, J = 15 Hz), 5.20 (bs, IH), 5.38 (s, IH), 7.01-7.34 (m, 4H). MS (m/z): 631 [M+H]⁺, 653 [M+Na]⁺.

Example 18

Synthesis of prodrug I-A1-PD2: To a solution of I-A1-PD1 (23.0 g, 36.45 mmol) in MeOH (250 mL) at 0 °C was added a solution of K₂CO₃ (7.54 g, 54.67 mmol) in water

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(55 mL) and stined for 10 min. The mixture was concentrated and purified by column chromatography to afford 18 g (83.8%) of the intermediate **I-A1-PD2**. ¹H-NMR (300 MHz, CDCl₃): δ 1.16 (t, 3H, J = 6 Hz), 2.35 (s, 3H), 2.84-2.88 (t, 2H, J = 6 Hz), 2.90-2.94 (t, 2H, J = 6 Hz), 3.44 (bs, 2H), 3.59-3.61 (bs, 5H), 3.84-3.91 (m, 2H), 4.0-4.03 (q, 2H, J = 3.11 Hz), 4.33 (bs, 2H), 4.69 (q, 2H, J = 15 Hz), 5.28 (bs, IH), 5.37 (s, IH), 7.12-7.36 (m, 4H). MS (ES⁺): m/z 589 [M⁺], 6.11 [M+Na]⁺.

Example 19

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Synthesis of prodrug I-Al-PD3:To a suspension of lamotrigine (13.09 g, 51.02 mmol) in toluene (100 mL) at 110 0 C was added a solution of LI-lxy (synthesized from LI-Ia and CDI, as described in Scheme 10) (16.27 g, 56.12 mmol) in THF (50 mL) and stirred at 110 0 C overnight. The reaction mixture was purified by column chromatography to give 6.0 g (24%) of I-A1-PD3 as a white solid. 1 H NMR (CD₃OD, 300 MHz) δ 2.04, (s, 3H), 2.96-3.02 (m, 4H), 4.30-4.35 (m, 2H), 4.45 (t, 2H), 7.38-7.45 (m, 2H), 7.67-7.69 (m, IH). MS: (ES⁺) m/z 477.9 (M+H)⁺, 499.9 (M+Na)⁺.

15 Example 20

Synthesis of prodrug **I-A1-PD4** :**To** a solution of **I-A1-PD3** (2 g, 4.18 mmol) in MeOH (15 mL) and THF (5mL) at 0 0 C was added a solution OfK $_{2}$ CO $_{3}$ (0.886 g, 6.276 mmol) in water (5 mL) and stirred at 0 0 C for 3 h. After usual aqueous work-up and chromatographic purification, 1.1 g (60%) of **I-A1-PD4** were obtained as a white solid. 1 H NMR (DMSO d $_{6}$, 300 MHz): δ 2.75-2.82 (m, 2H), 2.96-3.0 (m, 2H), 3.0 (s, IH), 3.6 (t, 2H, J = 6.3Hz), 4.30 (t, 2H, J = 6.6 Hz) 7.38-7.49 (m, 2H), 7.72-7.75 (m, IH). MS: (ES+) m/z 436 (M+H)+, 457 (M+Na)+.

Example 21

Syntheis of prodrug I-A1-PD5: To a solution of diphosgene (0.99 mL, 8.24 mmol) in DCM (3 mL) at 0 °C was added a solution of L312a (0.5 g, 2.74 mmol) and Hünig's base (2.39 mL, 13.73 mmol) in DCM (3 mL). The mixture was stirred at 0 °C for 30 min and concentrated to yield the intermediate L313a as a light-yellow semi-solid. A solution of a mixture of gabapentin ethyl ester hydrochloride (0.77g, 3.29 mmol) and Hünig's base (1.7 mL, 9.79 mmol) in DCM (6 mL) was added to the intermediate L313a at RT and stirred for 15 h. After usual aqueous work-up and chromatographic purification, 0.34 g (30 %) of I-A1-PD5 were obtained as a yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.26

(t, 3H, J = 6 Hz), 1.22-1.51 (m, 10 H), 2.26 (s, 2H), 2.96 (t, 2H, J = 6 Hz), 3.18 (d, 2H, J = 6 Hz), 3.49 (s, 2H), 3.82 (s, 3H), 4.09 (q, 2H, J = 6 Hz), 4.29 (t, 2H, J = 6 Hz), 5.39 (bs IH). MS: (ES⁺) m/z 408 (M+H)⁺, 430 (M+Na)⁺; (ESO m/z 406 (M-H)⁻.

Example 22

5 Synthesis of prodrug **I-A1-PD6: To** a solution of **I-A1-PD8** (1.0 g, 2.63 mmol) in DCM (3 mL) at RT was added CDI (0.46 g, 2.89 mmol) and stirred for 15 h. A suspension of serine methyl ester hydrochloride (0.61 g, 3.95 mmol) in DCM (4 mL) and TEA (1.1 mL, 7.90 mmol) was added and stirring continued for 15 h. After usual aqueous work-up and chromatographic purification, 0.706 g (51%) of **I-A1-PD6** were obtained as a colorless oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.25 (t, 3H, J = 7.1 Hz), 1.35-1.51 (m, 10H), 2.28(s, 2H), 2.91-2.98 (m, 4H), 3.16 (d, 2H, J = 9Hz), 3.78 (s, 3H), 3.94-4.38 (m, 9H), 5.5 (bs, IH), 6.0 (bs, IH). MS: (ES)⁺: m/z 525 (M+H)⁺, 547 (M+Na)⁺. (ES)⁻: m/z 523 (M-H)⁺.

Example 23

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Synthesis of prodrug **I-A1-PD7**: **To** a solutuion of **I-A1-PD8** (86 mg, 0.22 mmol) in DCM (9 mL) at RT was added CDI (40 mg, 0.24 mmol) and stirred for 15 h, after which a solution of dimethyl glutamate (80 mg, 0.45 mmol) and TEA (0.06 mL, 0.45 mmol) was added and stirred for 2 d. After usual aqueous work-up and chromatographic purification, 97 mg (74 %) of **I-A1-PD7** were obtained as a colourless oil. ^IH NMR (CDC1₃, 300 MHz): δ 1.25 (t, 3H, J=7.13 Hz), 1.36-2.5 (m, 16H), 2.93(t, 4H, J = 6.46 Hz), 3.19 (d, 2H, J = 6.67), 3.67 (s, 3H), 3.74 (s, 3H), 4.12 (q, 2H, J = 7.13 Hz), 4.25-4.44 (m, 5H), 5.4 (bs, IH), 5.65 (bs, IH). MS: (ES⁺) m/z 581 (M+H)⁺, 603 (M+Na)⁺; (ES⁻) m/z 571 (M-H)⁻.

Example 24

Synthesis of prodrug I-A1-PD9: To a suspension of gabapentin (10 g, 58.4 mmol) in THF (100 mL) at 0 °C was added IN NaOH (70 mL), followed by (Boc)₂O. The mixture was stirred at RT for 15 h. After washing with diethyl ether (100 mL x 2), the aqueous layer was acidified with solid KHSO₄ and extracted with EtOAc (100 mL x 2). Organic extracts were washed with brine (100 mL), dried over Na₂SO₄ and concentrated to afford 10.41g (68 %) of boc-protected gabapentin as a white solid.

A mixture of boc-protected gabapentin (5.0 g, 18.45 mmol) and CDI (3.59 g, 22.14 mmol) in DCM (75 mL) was stirred for 15 h. The mixture was concentrated and

dissolved in acetonitrile (50 mL), followed by the addition of 30 % aqueous solution of ammonia (50 mL) and stirred for 1.5 h at RT. After usual aqueous work-up, 4.5 g (90 %) of boc-protected gabapentin-amide were obtained as a white solid.

To a solution of boc-protected gabapentin-amide (2.59 g, 9.61 mmol) in DCM (12 mL) at 0 0 C was added solution of TFA (4mL) in DCM (4 mL) and stirred for 2.5 h at RT. The mixture was concentrated and dissolved in DCM (20 mL). This was treated successively with Hunig's base (6.7 mL, 38.46 mmol) and **LI-Ia** (1.45g, 7.39 mmol), and stirred at RT for 3 h. After usual aqueous work-up and chromatographic purification, 1.19 g (41 %) of **I-A1-PD9** were obtained as a yellow oil. 1 H NMR (CDCl₃, 300 MHz): δ 1.28-1.48 (m, 10H), 2.06 (s, 3H), 2.15 (s, 2H), 2.91 (t, 4H, J = 6.0 Hz), 3.23 (d, 2H, J = 6.0 Hz), 4.28-4.38(m, 4H), 5.7(bs, IH). MS: (ES)+ m/z 393(M+H)+; (ES)- m/z 392(M-H)-.

Example 25

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Synthesis of prodrug **I-A1-PD10**: A mixture of **I-A1-PD8** (1.Og, 2.63 mmol) and CDI (0.469 g, 2.89 mmol) in DMF (3 mL) was stirred for 12 h, after which N,N'dimethylethylenediamine (0.56mL, 5.26 mmol) and DMAP (0.32 g, 2.63 mmol) was added. The mixture was stirred for 4 h. After usual aqueous work-up and chromatographic purification, 0.763 g (59 %) of were obtained as a yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.25 (t, 3H, J = 6.0 Hz), 1.28-1.53 (m, 10H), 2.24 (s, 6H), 2.29 (s, 2H), 2.42 (t, 2H, J = 6.0 Hz), 2.92 (t, 4H, J = 6.0 Hz), 3.20(d, 2H, J = 6.0 Hz), 3.26 (q, 4H, J = 6.0 Hz), 4.13 (q, 2H, J = 7.0 Hz), 4.31 (t, 4H, J = 6.0Hz), 7.26 (bs, IH). MS: (ES)+ m/z 494 (M+H)+, 516 (M+Na)+; (ES)- m/z 492 (M-H)⁻.

Example 26

Synthesis of prodrug I-A1-PD11: A mixture of LI-Ia (2.0 g, 10.20 mmol) and CDI (1.98 g, 12.24 mmol) in DCM (12 mL) was stirred for 2 h and concentrated. The residue was dissolved in acetonitrile, and a suspension of gabapentin (2.62 g, 15.30 mmol) in saturated NaHCO₃ (15 mL) was added. The mixture was stirred at RT for 15 h. Acetonitrile was removed by distillation and the basic aqueous portion was washed with diethyl ether (100 mL x 2). The aqueous layer was acidified using 2N HCl and extracted in EtOAc (60 mL x 3). The organic layer was concentrated and the residue was purified by chromatographic purification, 1.76 g (43 %) of I-A1-PD11 were obtained as a

colorless oil. ${}^{1}H$ NMR (CDCl₃, 300 MHz): δ 1.27-1.68 (m, 10H), 2.07 (s, 3H), 2.31 (s, 2H), 2.92 (t, 4H, J = 6.0 Hz), 3.22 (d, 2H, J = 9.0 Hz), 4.31-4.35 (m, 4H), 5.43 (bs, IH). MS: (ES) 2 m/z 392 (M-H) 2 .

Example 27

Synthesis of prodrug **I-A1-PD13**: This prodrug was synthesized as shown in Scheme 12, Method B. Thus, to a solution of diphosgene (7.02 mL, 58.18 mmol) in DCM (20 mL) at 0 °C was added a solution of **LI-Ia** (5.71 g, 29.09 mmol) and Hünig's base (25.3 mL, 145.45 mmol) in DCM (30 mL) and stirred at RT for 40 min. The mixture was concentrated and a mixture of gabapentin ethyl ester hydrochloride (7.546 g, 32 mmol) and Hünig's base (11.15 mL, 64 mmol) in DCM (50 mL) was added and stirred overnight. Reaction mixture was concentrated and, after usual aqueous work-up and column chromatography, 8.42 g (67 %) of **I-A1-PD13** were obtained. ¹H NMR (CDCl₃, 300 MHz): δ 1.22 (t, 3H, J = 7.3 Hz), 1.27-1.68 (m, 10H), 2.06 (s, 3H), 2.27 (s, 2H), 2.91 (t, 4H, J = 6.6 Hz), 3.19 (d, 2H, J = 6.7 Hz), 4.08 - 4.15 (q, 2H, J = 7.1 Hz), 4.27-4.34 (q, 4H, J = 6.4 Hz), 5.4 (bs, 1H). MS: m/z 422 [M+H]⁺, 444 [M+Naf.

Example 28

Synthesis of prodrug **I-A1-PD8**: **To** an ice-cold solution of **I-A1-PD13** (8.0 g, 18.98 mmol) in MeOH (30 mL) was added a solution OfK₂CO₃ (5.24 g, 37.96 mmol) in water (38 mL). After 15 min, the mixture was concentrated. After usual aqueous work-up, 5.0 g (69 %) of **I-A1-PD8** were obtained. ¹H NMR (CDCl₃, 300 MHz): δ 1.25 (t, 3H, J = 7.11 Hz), 1.30-1.71 (m, 10H), 2.87-2.94 (m, 4H), 2.27 (s, 2H), 3.18 (d, 2H, J = 6.6 Hz), 3.87 (t, 2H, J = 5.7 Hz), 4.09-4.16 (q, 2H, J = 7.12 Hz), 4.31 (t, 2H, J = 6.51 Hz), 5.44 (bs, IH). MS: m/z 380 [M+H]⁺, 402 [M+Na]⁺.

Example 29

Synthesis of prodrug I-A1-PD12: To a solution of diphosgene (1.91 mL, 15.81 mmol) in DCM (20 mL) at 0 °C was added a solution of I-A1-PD8 (4 g, 10.54 mmol) and Hünig's base (5.5 mL, 31.62 mmol) in DCM (30 mL). The mixture was stirred at RT for 40 min, cooled to 0-5 °C, and dry ammonia gas was passed through it for 30 min. Reaction mixture was concentrated and, after usual aqueous work-up, 5.3 g (91 %) of I-A1-PD12
were obtained. ¹H NMR (CDCl₃, 300 MHz): δ 1.23 (t, 3H, J = 7.1 Hz), 1.27-1.79 (m,

10H), 2.28 (s, 2H), 2.91-3.03 (m, 4H), 3.19 (d, 2H, J = 6.7 Hz), 4.12 (q, 2H, J = 7.1 Hz), 4.31 (t, 4H, J = 6.4 Hz), 5.4 (t, IH, J = 6.0 Hz). MS: m/z 423 [M+H]⁺, 446 [M+Na]⁺.

Example 30

Synthesis of prodrug I-A1-PD14: Ethyl chloroformate (0.86 g, 7.9 mmol) was added to a solution of S-carbamoylmethyl-S-methylhexanoic acid (M. S. Hoekstra et al., Org. Proc. 5 Res. Dev. 1997, 1, 26-38) (1.0 g, 5.3 mmol) in THF (6 niL) at -10 °C, followed by TEA (2.4 mL, 17.0 mmol) and the mixture was stirred at -10 °C for 30 min. A solution of NaN₃ (1.73 g, 26.6 mmol) in water (10 mL) was added and stirred for 2h at -10 °C. The reaction mixture was brought to RT and extracted with EtOAc (3 x 25 mL), washed with water (2 x 25 mL), dried over Na₂SO₄ and concentrated. Toluene (20 mL) was added to 10 the residue and refluxed for 6 h. After cooling to RT, a solution of and SL-I (825 mg, 5.3 mmol) in DCM (10 mL) was added and stirred at RT for 14 h. After usual aqueous work-up and chromatographic purification, 318 mg (17 %) of I-A1-PD14 were obtained as a colorless oil. ¹H NMR (300 MHz, CDCl₂): δ 0.89-0.95 (m, 6H), 1.25-1.29 (m, 2H), 1.62-1.71 (m, IH), 2.04-2.1 (m, 1H), 2.38 (d, J = 5.2 Hz, 2H), 2.87-2.95 (m, 4H), 3.05-1.62-1.7115 3.36 (m, 2H), 3.88 (t, J = 5.7 Hz, 2H), 4.34 (t, J = 6.2 Hz, 2H), 5.06 (br s, IH). MS: m/z 338 [M]+.

Example 31

Synthesis of prodrug I-Al-PD15Ba: To a solution of I-A1-PD4 (0.350 g, 0.802 mmol) in DMF (3 mL) at RT was added CDI (0.195g, 1.204 mmol) and stirred at RT for 3 h. This mixture was added to a suspension of methanesulphonamide (0.304 g, 3.2 mmol) in DMF (4 mL) and NaH (0.153 g, 3.2 mmol) at 0 °C and stirred at RT for 4 h. The reaction was quenched with ice and, after usual aqueous work-up and chromatographic purification, 0.12 g (26%) of I-Al-PD15Ba were obtained as a white solid. ¹H NMR (CDCl₃+CD₃OD, 300MHz): δ 2.83- 2.90 (m, 4H), 3.10 (s, 3H), 4.26-4.36 (m, 4H), 7.19-7.28 (m, 2H), 7.48-7.51 (m, IH). MS: (ES [†]) m/e 556.96 (M+H)⁺, 578.92 (M+Na)⁺.

Example 32

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Synthesis of prodrug I-A1-PD16: CDI (4 g, 24.7 mmol) was added to a solution of LI-2c (4 g, 15.8 mmol) in THF (30 mL) and stirred at RT for 2 h. Then, a solution of gabapentin (4 g, 23.4 mmol) in 20 % NaHCO $_3$ solution (10 mL) was added and stirred overnight at RT. The reaction mixture was neutralized with 0.5N HCl (pH \sim 4), extracted

with EtOAc (4 x 40 mL), dried over Na₂SO₄, concentrated and purified by column chromatography to afford 4.7 g (66 %) of **I-S12-PD2** as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 1.45-1.49 (br s, 19H), 2.35 (s, 2H), 2.80-2.97 (m, 4H), 3.24 (d, J = 5.7 Hz, 2H), 3.46 (m, 2H) 4.33 (t, J = 5.7 Hz, 2H), 5.0 (br s, IH), 5.71 (br s, IH). MS: (m/z) [ES]⁻ 449.1 [M-H]⁺; [ES]⁺ 451.2 [M+H]⁺.

EtOAc saturated with HCl gas (5mL) was added to **I-S12-PD2** (0.55 g, 1.22 mmol) and stirred at RT for 10 h. Solvent was removed under reduced pressure and purified by preparative HPLC to give 425 mg (90 %) of **I-A1-PD16** as a colorless liquid. ¹H NMR (300 MHz, CD₃OD): δ 1.52 (br s, 10H), 2.4 (s, 2H), 2.98-3.09 (m, 4H), 3.27-3.34 (m, 2H), 3.61 (s, 2H), 4.5 (t, J = 6.0 Hz, 2H). MS: [ES]⁺ m/z 351.0 [M+H]⁺.

Example 33

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Synthesis of prodrug **I-A2-PD1**: To a solution of levetiracetam (1.0 g, 5.87 mmol) in DCE (20 mL) and DCM (4 mL) was added oxalyl chloride (0.61 mL, 7.05 mmol), and heated at 70 $^{\circ}$ C for 8h. Reaction mixture was cooled and added to a solution of SL-I (1.81 g, 11.75 mmol) in DCM (15 mL) and stirred at RT overnight. After chromatographic purification, 1.13 g (41%) of **I-A2-PD1** were obtained. 1 H NMR (CDCl₃, 300 MHz): δ (ppm): 0.87 (t, J = 7.3 Hz, 3H), 1.84-2.04 (m, 4H,), 2.41 (t, J = 6.9 Hz, 2H,), 2.69 (bs, IH), 2.87-2.95 (m, 4H), 3.02-3.11 (m, IH), 3.65-3.75 (m, IH), 3.85-3.95 (m, 2H), 4.06-4.12 (m, IH), 4.34-4.41 (m, 2H), 8.69 (bs, IH). MS: (ES⁺): m/z 351.0 [M+H]⁺; 372.9 [M+Na]⁺.

Example 34

Synthesis of prodrug I-A3-PD1: To a solution of I-S13-PD1 (which was synthesized as described in Example 37, Step 2) (215 mg, 0.292 mmol) and triisopropylsilane (60 μL) in 0.75 mL of DCM was added 20 % TFA in DCM (0.5 mL) and stirred at RT for 90 min.

The mixture was concentrated and the residue purified by column chromatography to give 65 mg (46%) of I-A3-PD1. ¹H-NMR (300 MHz, CDCl₃): δ 2.51 (s, 3H), 2.85-2.92 (m, 4H), 3.87 (t, 2H, J = 4.5 Hz), 4.37 (t, 2H, J = 6.0 Hz), 7.25-7.43 (m, 7H), 8.01 (d, 2H, J = 3.0 Hz). MS (m/z): 493 [M-H]⁻, 517 [M+Naf.

Example 35

30 Synthesis of prodrugs I-A3-PD3a and I-A3-PD3b: Step 1: DSC (210 mg, 0.824 mmol) and TEA (0.230 mL, 1.64 mmol) were added to a solution of methyl [(2-

hydroxy ethyl)dithio]acetate (100mg, 0.549 mmol) in acetonitrile (1 mL) at O ⁰C and stirred at RT for 3h. The mixture was concentrated and the residue dissolved DCM. Usual aqueous work-up and chromatographic purification gave the crude intermediate.

- Step 2: TEA (24mg, 0.236 mmol) and DMAP (13 mg) were added to a mixture of valdecoxib (62mg, 0.195 mmol) and the product obtained from step 1 above in THF (1 mL) and stirred at RT for 3 d. The mixture was concentrated and the residue dissolved in EtOAc. After usual aqueous work-up and chromatographic purification, 53 mg (52%) of I-A3-PD3a obtained. 1 H- NMR (300 MHz, CDCl₃): δ 2.51 (s, 3H), 2.97 (t, 2H, J = 6.0 Hz), 3.48 (s, 2H), 3.76 (s, 3H), 4.37 (t, 2H, J = 6.0 Hz), 7.33-7.40 (m, 7H), 8.03-8.12 (m,
- Step 3: The above material was converted to the corresponding mono-, and/or di-sodium salt forms I-A3-PD3b by using standard methods. Thus, to a cold solution of the above compound (150 mg, 0.287 mmol) in THF (1 mL) was added IM LiOH solution (28 mg in ImL water) and stirred overnight at RT. The mixture was concentrated, the residue diluted with water, acidified with IN HCl (~3 ml, pH ~3) and extracted with EtOAc. After usual aqueous work-up and chromatographic purification, 20 mg (13%) of product were obtained. ¹H- NMR (300 MHz, CDCl₃): δ 2.49 (s, 3H), 2.70-2.89 (m, 4H), 4.23-4.33 (m, 2H), 7.28-7.38 (m, 7H), 8.01-8.03 (m, 2H).

Example 36

2H). MS (m/z): 521 [M-H]⁻.

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- 20 Synthesis of prodrug I-A3-PD4: This prodrug was synthesized as described in Scheme 13, Method B.
 - Step 1: Synthesis of intermediate LI-8:
 - CDI (1.65 g, 10.19 mmol) was added to a solution of LI-Ia (2.0 g, 10.19 mmol) in DMF (10 mL) and stirred at RT for 3 h. N,N-Dimethylethylenediamine (1.2 mL, 11.12 mmol)
- was added and stirred for 2 h. The mixture was concentrated and the residue taken up in EtOAc. After usual aqueous work-up and chromatographic purification, 1.3 g (41%) LI-8 were obtained. ¹H-NMR (300 MHz, CDCl₃): δ 2.07 (s, 3H), 2.31 (bs, 6H), 2.51 (t, 2H, J = 6.0 Hz), 2.91 (t, 4H, J = 6.0 Hz), 3.31 (q, 2H, J = 6.0 Hz), 4.28-4.34 (m, 4H), 5.52 (bs, IH). MS (m/z): 333 [M+Na]⁺.
- 30 Step 2: Synthesis of intermediate LI-9: To a solution of LI-8 (1.3 g, 4.18 mmol) in MeOH (7 mL) was added a 1.25M solution Of K₂CO₃ (5 mL) and stirred at RT for Ih.

The mixture was concentrated and the residue was taken up in DCM. After usual aqueous work-up, 1.02 g (91%) of product were obtained. 1 H-NMR (300 MHz, CDCl₃): δ 2.29 (s, 6H), 2.54 (t, 2H, J = 6.0 Hz), 2.86-2.99 (m, 4H), 3.33 (q, 2H, J = 5.0 Hz), 3.86 (t, 2H, J = 6.0 Hz), 4.31 (t, 2H, J = 6.0 Hz), 5.71 (bs, IH). MS (m/z): 269 [M+H]⁺. This product was used as such in the next step.

Step 3: Synthesis of intermediate LI-10: A solution of LI-9 (1.02 g, 3.80 mmol) in acetonitrile (10 niL) was added to a cold solution of DSC (1.46 g, 5.70 mmol) in acetonitrile (50 mL) followed by TEA (1.58 ml, 11.40 mmol), and stirred overnight at RT. The mixture was concentrated and the residue was taken up in DCM. After usual aqueous work-up, 1.33 g (85%) of LI-10 were obtained.

Step 4: Synthesis of I-A3-PD4: TEA (0.194 mL, 1.39 mmol) and DMAP (73 mg, 0.6 mmol) were added to a solution of LI-10 (1.33 g, 3.24 mmol) and valdecoxib (364 mg, 1.16 mmol) in THF (6 mL) and stirred at RT for 5 d. The mixture was concentrated and the residue was taken up in DCM. After usual aqueous work-up and chromatographic purification, 177 mg (12 %) of LI-10 were obtained. ¹H-NMR (300 MHz, CDCl₃): δ 2.46 (s, 3H), 2.85-2.95 (m, 10H), 3.28 (t, 2H, J = 6.0 Hz), 3.65 (q, 2H, J = 3.0 Hz), 4.22-4.28 (m, 4H), 7.22-7.41 (m, 7H), 7.94 (d, 2H, J = 9.0 Hz). MS (m/z): 609 [M+H]⁺. This product was converted to water-soluble hydrochloride salt form using standard methods. Example 37

20 Synthesis of prodrug I-A3-PD5: This prodrug was synthesized as shown in Scheme 13, Method B.

Step 1: Synthesis of prodrug intermediate LI-lxy:

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A solution of LI-Ic (1.0 g, 2.52 mmol) in acetonitrile (10 mL) was added to a solution of DSC (0.96 g, 3.78 mmol) in acetonitrile (20 mL) and stirred for 10 min. After cooling to 0 °C, TEA (1 ml, 7.57 mmol) was added and stirred at RT for 3.5 h. The solution was concentrated and the residue was taken up in DCM. After usual aqueous work-up, the crude product obtained was used as such in the next step.

Step 2: Synthesis of prodrug intermediate **I-S13-PD1**: A mixture of valdecoxib (280 mg, 0.892 mmol), DMAP (56 mg, 0.5 mmol) and TEA (150 μ L, 1.06 mmol) in THF (5 mL) was stirred at RT for 4.5 d. The mixture was concentrated and the residue dissolved in EtOAc. After usual aqueous work-up and chromatographic purification, 354 mg (54 %) of **I-S13-PD1** were obtained. ¹H-NMR (300 MHz, CDCl₃): δ 2.47 (s, 3H), 3.32-3.41 (m, 4H), 4.28 (t, 2H, J = 6.0 Hz), 4.47 (t, 2H, J = 6.0 Hz), 7.20-7.61 (m, 22H), 8.00 (d, 2H, J = 9.0 Hz). MS (m/z): 736 [M-H]^T.

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- Step 3: Synthesis of intermediate I-A3-PD1: To a solution of I-S13-PD1 (215 mg, 0.292 mmol) and triisopropylsilane (60 μL) in 0.75 ml of DCM was added 20%TFA in DCM (0.5 mL) and stirred at RT for 90 min. The mixture was concentrated and the residue purified by column chromatography to give 65 mg (46%) of I-A3-PD1. ¹H-NMR (300 MHz, CDCl₃): δ 2.51 (s, 3H), 2.85-2.92 (m, 4H), 3.87 (t, 2H, J = 4.5 Hz), 4.37 (t, 2H, J = 4.5 Hz), 7.25-7.43 (m, 7H), 8.01 (d, 2H, J = 3.0 Hz). MS (m/z): 493 [M-H]⁻, 517 [M+Na]⁺.
- Step 4: Synthesis of I-A3-PD5-Me-ester: CDI (40mg, 0.243 mmol) was added to a solution of I-A3-PD1 (IOOmg, 0.202 mmol) in DMF (0.5 mL) and stirred at RT for 2.5 h. To this were added a solution of dimethyl glutamate (53 mg, 0.303 mmol) in DMF (0.3 mL) and DMAP (37 mg, 0.303 mmol) and stirred overnight at RT. The mixture was dissolved in EtOAc and, after usual aqueous work-up and chromatographic purification, 110 mg (78%) of I-A3-PD5-Me-ester were obtained ¹H- NMR (300 MHz, CDCl₃): δ 1.71-1.91 (m, 2H), 2.38-2.42 (m, 2H), 2.44 (s, 3H), 2.84-2.95 (m, 4H), 3.66 (s, 3H), 3.67 (s, 3H), 4.31¹.34 (m, 4H), 4.43-4.52 (m, IH), 7.31-7.41 (m, 7H), 8.02 (d, 2H, J = 9.0 Hz). MS (m/z): 694 [M-H]-.
- Step 5: Synthesis of prodrug **I-A3-PD5:** IN Lithium hydroxide (1.2 mL, 1.2 mmol) was added to a solution of **I-A3-PD5-Me-ester** (100 mg, 0.144 mmol) in THF (0.4 mL) at 0 ⁰C and the mixture allowed to attain ambient temperature. After 30 min, the mixture was

concentrated and the residue diluted with water. Acidification with IN HCl, followed by extraction with EtOAc, usual aqueous work-up and chromatographic purification gave 26 mg (26%) of **I-A3-PD5.** 1 H-NMR (300 MHz, CD₃OD): δ 1.82-1.97 (m, IH), 2.05-2.13 (m, IH), 2.30-2.40 (m, 2H), 2.48 (s, 3H), 2.84 - 2.94 (m, 4H), 4.06 - 4.08 (m, IH), 4.15 - 4.22 (m, 4H), 7.30 (d, 2H, J = 9 Hz), 7.35 - 7.41 (m, 5H), 7.92 (d, 2H, J = 9.0 Hz). MS (nVz): $666 \, [M-H]^{-}$.

Example 38

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Synthesis of prodrug I-H1-PD1: This prodrug was synthesized as shown in Scheme 14, Method B.

Step 1: A solution of metronidazole (5.0 g, 29.22 mmol) and CDI (5.21 g, 32.2 mmol) in DCM (100 mL) was stirred overnight at RT. After usual aqueous work-up, 7.32 g of the imidazolide of metronidazole were obtained, which was used as such in the next step.

Step 2: A solution of the imidazolide of metronidazole (7.32 g) in DMF (30 mL) was

added to a solution of **SL-I** (6.39 g, 41.43 mmol) in DMF (10 mL) and stirred at 60 $^{\circ}$ C for 2.5 h. The mixture was concentrated and the residue was taken up in DCM. After usual aqueous work-up and chromatographic purification, 6.32 g (65%) of **I-H1-PD1** were obtained. 1 H-NMR (300 MHz, CDCl₃): δ 2.15 (bs, IH), 2.52 (s, 3H), 2.83-2.92 (m, 4H), 3.84-3.92 (m, 2H), 4.34 (t, 2H, J = 6.0 Hz), 4.51 (t, 2H, J = 3.0 Hz), 4.53-4.62 (m, 2H), 7.96 (s, IH).

20 Example 39

Synthesis of I-H1-PD14: This prodrug was synthesized as described in Scheme 14, Method C. Thus, TEA (0.915 mL, 6.56 mmol) and DMAP (cat.) were added to a solution of LI-2C.TFA (541 mg, 3.94 mmol) and the imidazolide of metronidazole (synthesis described in Example 114) (870 mg, 3.28 mmol) in DMF (2 mL) and the mixture was heated at 60 0 C for 3.5 h. The mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, gave 546 mg (48%) of I-H1-PD14. 1 H-NMR (300 MHz, CDCl₃): δ 2.48 (s, 3H), 2.76-2.96 (m, 4H), 3.46 (q, 2H, J = 6.0 Hz), 3.87 (t, 2H, J = 6.0 Hz), 4.41 (t, 2H, J = 6.0 Hz), 4.57 (t, 2H, J = 4.5 Hz), 7.90 (s, IH). MS (m/z): $351[M+H]^{+}$.

30 Example 40

Synthesis of prodrug **I-H1-PD2**: This prodrug was synthesized as described in Scheme 14, Method C. Thus, CDI (180 mg, 1.1 mmol) was added to a solution of **I-H1-PD14** (350 mg, 1.0 mmol) in DMF (2 mL) and stirred at RT for 4 h. NJSI-Dimethylethylenediamine (88 mg, 1.0 mmol) was added and stirred for 3 h. The mixture was concentrated and the residue purified by column chromatography to afford 175 mg (38%) of **I-H1-PD2**. ¹H-NMR (300 MHz, CDCl₃): δ 2.28 (s, 3H), 2.49 (s, 6H), 2.51-2.55 (m, 2H), 2.81 (t, 2H, J = 6.0 Hz), 2.89 (t, 2H, J = 6.0 Hz), 3.27-3.33 (m, 2H), 3.46 (q, 2H, J = 6.0 Hz), 4.29 (t, 2H, J = 6.0 Hz), 4.40 (t, 2H, J = 4.5 Hz), 4.57 (t, 2H, J = 4.5 Hz), 5.55 (bs, IH), 7.94 (s, IH). MS (m/z): 465[M+H] ⁺. This product was converted to watersoluble hydrochloride salt form using a standard method.

Example 41

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Synthesis of prodrug I-H1-PD5: This prodrug was synthesized as described in Scheme 14, Method A.

Step 1: Synthesis of Intermediate **I-S14-PD1:** A solution of the imidazolide of **LI-Ic** (1.6 g, 2.98 mmol) in acetonitrile (10 mL) was added to a solution of zudovudine (1.0 g, 3.74 mmol) in acetonitrile (20 mL) at RT, followed by DMAP (0.914 g, 7.48 mmol) and stirred for 24 h. The mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, gave 1.62 g (79%) of intermediate **I-S14-PD1.** ¹H-NMR (300 MHz, CDC1₃): δ 1.95 (s, 3H), 2.35-2.45 (m, 2H), 2.78 (t, 2H, J= 6.6 Hz), 2.87 (t, 2H, J= 6.33 Hz), 3.38 (t, 2H, J= 6.33 Hz), 4.05 (m, IH), 4.25 (m, IH), 4.35 - 4.41 (m, 4H), 6.20 (t, IH, J= 6.16), 7.21- 7.33 (m, 9H), 7.42-7.48 (m, 6H) and 8.49 (s, IH). MS (m/z): 712 [M+Na]⁺.

Step 2: Synthesis of **I-H1-PD5**: To a solution of **I-S14-PD1** in DCM (15 mL) were added triisopropylsilane (0.446 ml, 2.17 mmol), followed by 10% TFA in DCM (15 mL) and stirred at RT for 30 min. The mixture was concentrated and purified by column chromatography to afford 0.68 g (70%) of prodrug **I-H1-PD5**. ¹H-NMR (300 MHz, CDCl₃): δ 1.93 (s, 3H), 2.30 (bs, IH), 2.41-2.48 (m, 2H), 2.88 (t, 2H, J= 6.1 Hz), 2.96 (t, 2H, J= 6.6 Hz), 3.88 (t, 2H, J= 5.8 Hz), 4.05 (m, IH), 4.29 (m, IH), 4.30-4.48 (m, 4H), 6.18 (t, IH, J= 6.3 Hz), 7.34 (s, IH) and 9.11 (s, IH). MS (m/z): 448 [M+H]⁺, 470 [M+Na]⁺.

Synthesis of prodrug I-S22-PD1: This prodrug was synthesized in two steps as shown in Scheme 22.

Step 1: To a solution of diphosgene (0.35 mL, 2.93 mmol) in DCM (3mL) was added a solution of LI-Id (0.404 mg, 1.75 mmol), Hunig's base (0.765 mL, 4.39 mmol) and the 5 resulting mixture was stirred at RT for 45 min. The mixture was concentrated, the residue dissolved in DCM (5 mL), cooled in an ice-bath and treated with a solution of paclitaxel (500 mg, 0.585 mmol), Hunig's base (0.765 mL, 4.39 mmol) and DMAP (cat.) in DCM (5 mL) over 5 min and the resulting mixture was stirred at RT for 2 h. The mixture was purified by column chromatography to give 519 mg (78%) of the protected intermediate 10 **S22-I2** as an off-white solid. ¹H NMR (500 MHz, CDCl₃): δ 1.14 (s, 3H), 1.28 (s, 3H), 1.68 (s, 3H), 2.04 (s, 3H), 2.23 (s, 3H), 2.37 - 2.45 (m, 2H), 2.46 (s, 3H), 2.50 - 2.52 (m, 2H), 2.90 - 2.95 (m, 4H), 3.82 (d, IH, J = 7.0 Hz), 4.05 (s, 2H), 4.21 (d, IH, J = 8.5 Hz), 4.32 (d, IH, J = 8.0 Hz), 4.40 - 4.42 (m, 5H), 4.97 (d, IH, J = 9.5 Hz), 5.29 (s, IH), 5.43 15 (d, IH, J = 2.5 Hz), 5.69 (d, IH, J = 7.0 Hz), 6.00 (dd, IH, J = 9.5 Hz, 2.5 Hz), 6.26-6.29 (m, 2H), 7.02 (d, 1H, J = 9.5 Hz), 7.38 - 7.61 (m, HH), 7.75 (d, 2H, J = 7.5 Hz), 8.15 (d, 2H,2H, J = 7.5 Hz).

Step 2: To an ice-cold solution of **S22-I2** (60 mg, 0.0532 mmol) in MeOH (1 mL) was added 2 drops of methanol saturated with ammonia gas and the resulting mixture was stirred for 1 h. The reaction mixture was purified by column chromatography to give 38 mg (69%) of **I-S22-PD1** as an off white solid. ¹H NMR (500 MHz, CDCl₃): δ 1.14 (s, 3H), 1.23 (s, 3H), 1.68 (s, 3H), 1.91 (s, 3H), 2.23 (s, 3H), 2.38 - 2.42 (m, 2H), 2.46 (s, 3H), 2.50 - 2.58 (m, 2H), 2.84 (t, 2H, J = 5.4 Hz), 2.94 (t, 2H, J = 6.5 Hz), 3.82 (t, 3H, J = 6.0 Hz), 4.20 (d, IH, J = 8.5 Hz), 4.31 (d, IH, J = 8.5 Hz), 4.35 - 4.41 (m, 3H), 4.97 (d, IH, J = 7.5 Hz), 5.44 (d, IH, J = 2.5 Hz), 5.69 (d, IH, 7.0 Hz), 6.0 (dd, IH, J = 9.25 Hz, 2.25 Hz), 6.22-6.29 (m, 2H), 7.08 (d, IH, J = 9.5 Hz), 7.36-7.60 (m, HH), 7.78 (d, 2H, **J** = 7.5 Hz), 8.14 (d, 2H, **J** = 7.5 Hz).

Example 43

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Synthesis of prodrug **I-S22-PD2:** To a solution of **I-S22-PD1** (38 mg, 0.0367 mmol) in acetonitrile (0.6 mL) was added succinic anhydride (5 mg, 0.044 mmol) and DMAP (cat.). The resulting mixture was stirred overnight at RT and purified by column

chromatography to give 12 mg (29%) of prodrug **I-S22-PD2** as an off white solid. 1 H NMR (500 MHz, CDCl₃): δ 1.14 (s, 3H), 1.25 (s, 3H), 1.68 (s, 3H), 1.91 (s, 3H), 2.22 (s, 3H), 2.36 - 2.41 (m, IH), 2.49 (s, 3H), 2.57 - 2.63 (m, 5H), 2.86 - 2.89 (m, 2H), 2.93 (t, 2H, J = 6.5 Hz), 3.79 (d, IH, J = 7.0 Hz), 4.20 - 4.44 (m, 7H), 4.98 (d, IH, J = 8.0 Hz), 5.53 (d, IH, 3.0 Hz), 5.69 (d, IH, J = 7.0 Hz), 6.02 (dd, IH, J = 9.5 Hz, J = 3.0 Hz), 6.26-6.29 (m, 2H), 7.20 (d, IH, J = 9.0 Hz), 7.33 - 7.62 (m, HH), 7.74 (d, 2H, J = 7.5 Hz), 8.14 (d, 2H, J = 7.5 Hz). MS (ES⁺) m/z: 1134.44 [M+H]⁺; 1156.56 [M+Na]⁺.

Water solubility: Paclitaxel and its prodrug I-S22-PD2 (2 mg each) were suspended in 1 mL water or PBS-buffer (pH 7.4). The suspensions were sonicated for 15 min and centrifuged (13,000 g) for 10 min. The supernatant was analyzed using HPLC.

HPLC: Waters RP18 column (150 x 3.9 mM, X-Terra); DAD-HP Agilent (Model 1100); eluent: CH₃CNrH₂O (gradient 0-100% acetonitrile in 0-15 min). The uv-detector was set at 210 nM. The concentrations were determined by measuring the relative area of paclitaxel or I-S22-PD2. It was observed that the solubility of I-S22-PD2 was 20 times more than that of paclitaxel. (i.e, ~0.2 mg/mL).

The following double/mutual prodrugs (Examples 44 - 80) were synthesized by the methods depicted in Schemes 17-21, using appropriate therapeutic agents and obvious modifications:

Example 44

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20 Synthesis of mutual prodrug of desloratidine and pseudoephedrine (I-AA-MPD1):

This mutual prodrug was synthesized as depicted in Scheme 21. The compound I-AA-MPD1 was obtained as a colorless gum. ¹H-NMR (300 MHz, CDCl₃): δ 1.00 (d, 3H, J = 6.9 Hz), 2.27-2.51 (m, 4H), 2.74-2.97 (m, 9H), 3.28-3.41(m, 4H), 3.79 (bs, 2H), 4.28-4.30 (m, 4H), 4.57 (m, IH), 7.04-7.44 (m, 9H), 8.26-8.33 (m, 2H). MS (m/z): 682 [M+H]⁺.

Example 45

Synthesis of mutual prodrug of amlodipine and lisinopril (I-AA-MPD2):

Step 1: Synthesis of diethyl ester of lisinopril:

To a suspension of lisinopril (10.0 g, 22.62 mmol) in ethanol (150 mL) was added SOCl₂ (4.95 mL, 67.94 mmol) and refluxed for 1.5 h. An additional 1 mL of SOCl₂ was added to the mixture every hour for 4 h. The mixture was concentrated and azeotroped with

benzene. The resulting hydrochloride was basified with saturated NaHCO 3 and extracted with EtOAc. Usual aqueous work-up gave 12.86 g of lisinopril diethyl ester, which was used without purification. ¹H-NMR (300 MHz, CDCl₃): δ 1.23-1.64 (m, 10H), 1.89-2.3 (m, 6H), 2.63-2.66 (m, 2H), 2.80 (bs, 2H), 3.19 (t, 2H, J = 7.5 Hz), 3.36-3.59 (m, 6H), 4.12-4.19 (m, 4H), 4.4-4.5 (m, IH), 7.14-7.28 (m, 5H). MS [m/z]: 462.4 [M+H]⁺.

Step 2: Synthesis of I-AA-MPD2: CDI (1.23 g, 7.64 mmol) was added to a solution of I-A1-PD2 (Example 18) (3.0 g, 5.09 mmol) in DMF (10 rxiL) and stirred RT for 3.5 h. A solution of lisinopril diethyl ester (2.34 g, 5.09 mmol) in DMF (5 niL) was added and stirred at 65 °C for 8 h. The reaction was quenched with brine and taken up in EtOAc.

After usual aqueous work-up and chromatographic purification, 2.5 g (45%) of I-AA-10 **MPD2** were obtained. ¹H-NMR (300 MHz, CDCl₃): δ 1.17 (t, 3H, J = 7.5 Hz), 1.24-1.30 (m, 7H), 1.45-1.80 (m, 7H), 1.90-2.30 (m, 7H), 2.36 (s, 3H), 2.70 (bs, 2H), 2.89-2.95 (m, 4H), 3.10-3.20 (bs, 3H), 3.40-3.70 (m, 9H), 4.00-4.40 (m, 10H), 4.47-4.53 (m, 1H), 4.68-4.73 (q, 2H, J = 13 Hz), 5.30 (bs, IH), 5.39 (s, IH), 5.65 (bs,IH), 7.15-7.36 (m, 9H). MS (m/z): 1076 [M+H]+, 1098 [M+Naf.

Example 46

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Synthesis of mutual prodrug of amlodipine and losartan (I-AA-MPD3a):

This mutual prodrug was synthesized as described in Example 34, with obvious modifications, using the appropriate amino containing therapeutic agents. The product 1-AA-MPD3a was obtained as a cream color solid. ¹H-NMR (300 MHz, CDCl₃): δ 0.86 (t, 3H, J = 6.6Hz), 1.16 (t, 3H, J = 7.1 Hz), 1.31 (m, 2H), 1.60 (m, 2H), 2.31 (s, 3H), 2.48 (t, 2H, J = 7.9 Hz), 2.80-2.92 (m, 4H), 3.40 (m, 4H), 3.56 (s, 3H), 4.01 (m, 2H), 4.32 (m, 4H), 4.68 (q, 2H, J = 6.5 Hz), 5.00 (s, 2H), 5.14 (s, 2H), 5.37 (s, IH), 6.90 (d, IH, J = 7.8 Hz), 7.02- 7.22 (m, 5H), 7.33-7.43 (m, 3H), 7.50-7.60 (m, 2H). MS (m/z): 1037 [M-H].

Example 47 25

Synthesis of mutual prodrug of celecoxib and valdecoxib (I-AA-MPD4):

This mutual prodrug was synthesized by reacting the imidazolide intermediate of I-A3-PDI with valdecoxib according to method described in Scheme 17 with appropriate modifications. This mutual prodrug I-AA-MPD4 was obtained as a white solid. 1H-NMR (300 MHz, CDCl₃): δ 2.16 (s, 3H), 2.29 (s, 3H), 2.71 (bs, 4H), 4.14 (bs, 4H), 6.69 (s, 2H), 7.02-7.33 (m, 14H), 7.97 (d, 3H, J = 9.0 Hz). MS (m/z): 900 [M-H].

Synthesis of double prodrug of valdecoxib (I-AA-MPD5):

This double prodrug was synthesized by reacting **I-A3-PD1** and valdecoxib using the method B described in Scheme 13. The double prodrug **I-AA-MPD5** was obtained as an off white solid. 1 H-NMR (300 MHz, CDCl₃): δ 2.40 (s, 6H), 2.82 (bs, 4H), 4.20 (bs, 4H), 7.20-7.35 (m, 14H), 7.97 (d, 4H, **J** = 9.0 Hz). MS (m/z): 833[M-H]⁻.

Example 49

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Synthesis of double prodrug of valdecoxib (I-AA-MPD8a):

This mutual prodrug was synthesized using succinic anhydride and valdecoxib according to method B described in Scheme 13 with appropriate modifications. This double prodrug I-AA-MPD8a was obtained as an off-white solid. ¹H-NMR (300 MHz, CDCl₃): δ 2.46 (s, 6H), 2.58 (s, 4H), 7.25-7.37 (m, 16H), 7.95 (d, 2H, J = 9.0 Hz). MS (m/z): 709 [M-H]⁻.

Example 50

15 Synthesis of double prodrug of valdecoxib (I-AA-MPD8b):

This mutual prodrug was synthesized using glutaric anhydride and valdecoxib according to method B described in Scheme 13 with appropriate modifications. This double prodrug **I-AA-MPD8b** was obtained as a colorless gum. I H-NMR (300MHz, CDCl₃+ CD₃OD): δ 1.68-1.74 (m, 2H), 2.15 (t, 4H, J = 4.5 Hz), 2.38 (s, 6H), 7.01 (bs, IH), 7.17-7.30 (m, 14H), 7.50 (bs, IH), 7.88 (d, 4H, J = 8.58 Hz). MS (m/z): 723 [M-H]^T.

Example 51

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Synthesis of mutual prodrug of olanzapine and fluoxetine (I-AA-MPD9):

This mutual prodrug was made according to Scheme 17 with appropriate modifications. This mutual prodrug **I-AA-MPD9** was obtained as a yellow gum. 1 H-NMR (300 MHz, CDCl₃): δ 2.05-2.20 (m, 2H), 2.40 (s, 3H), 2.44 (s, 3H), 2.50-2.90 (m, 12H), 3.30-3.80 (m, 4H), 4.10-4.50 (m, 4H), 5.20 (bs, IH), 6.42 (s, IH), 6.87 (d, 2H, J = 8.52 Hz), 7.04-7.36 (m, 9H), 7.42 (d, 2H, J = 8.67 Hz). MS (m/z): 828 [M+H]⁺.

Example 52

Synthesis of double prodrug of gabapentin (I-AA-MPDIOa):

30 This double prodrug was synthesized as described below:

- Step 1: A solution of SL-I (3.0 g, 19.4 mmol) in DMF (5 mL) was added to a suspension of CDI (9.46 g, 5.83 mmol) in DMF (15 mL) and stirred at RT for 20 h. The mixture was concentrated and the residue purified by column chromatography. The bis-imidazolide obtained was used as such in the next step.
- Step 2: A solution of the bis-imidazolide (1.0 g, 2.91 mmol) in acetonitrile (3 mL) was added to a dispersion of gabapentin (1.49 g, 8.75 mmol) in IN NaHCO₃ (8 mL) and stirred at RT for 3 d. The mixture was diluted with water, acidified with 2N HCl and extracted with EtOAc. After usual aqueous work-up and chromatographic purification, 1.04 g (65%) of pure I-AA-MPD10 was obtained. ¹H-NMR (300 MHz, CDCl₃): δ 1.20-1.47 (m, 20H), 2.33 (s, 4H), 2.96 (t, 4H, J = 5.48 Hz), 3.23 (d, 4H, J = 6.5 Hz), 4.31 (t, 4H, J = 6.0 Hz), 5.55 (t, 2H, J = 6.6 Hz), ESI MS (m/z): 547 [M-H]^T.

Synthesis of double prodrug of gabapentin ethyl ester (I-AA-MPDIOb):

A mixture of **I-A1-PD8** (2.0 g, 5.26 mmol) and Hunig's base (2.75 mL, 15.8 mmol) in DCM (8 mL) was added to a solution of diphosgene (1.27 mL, 10.53 mmol) in DCM (4 mL) at 0 °C and stirred for 30 min. The mixture was concentrated, dissolved in DCM (10 mL) and treated with a solution of gabapentin ethyl ester hydrochloride (1.86 g, 7.88 mmol) and Hunig's base (2.74 mL, 15.77 mmol) in DCM (10 mL). The mixture was stirred for 3 h. After usual aqueous work-up, the crude material was purified by preparative HPLC to afford 2.2 g (69 %) of **I-AA-MPDIOb** as a colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ 1.25 (t, 6H, J = 6.0 Hz), 1.35-1.67 (m, 20H), 2.33 (s, 4H), 2.91 (t, 4H, J = 6.0 Hz), 3.18 (d, 4H, J = 6.0 Hz), 4.12 (q, 4H, J = 6.0 Hz), 4.29 (t, 4 H, J = 6.0 Hz) 5.42 (bs, 2H). MS: ES+ m/z 605 [M+H]⁺, 627 [M+Na]⁺.

Example 54

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25 Synthesis of mutual prodrug of lamotrigine and gabapentin (I-AA-MPD11):

To a solution of I-A1-PD4 (4.5 g, 10.32 mmol) in acetonitrile (40 mL) at RT was added CDI (2.0 g, 12.38 mmol) and stirred for 3 h. To this was added a solution of gabapentin (2.12 g, 12.38 mmol) in 10 ml of 1% NaHCO₃ solution and the mixture was stirred at RT for 24 h. After usual aqueous work-up and chromatographic purification, 2.6 g (40 %) of I-AA-MPD11 was obtained as an off white solid. ¹H NMR (CD₃OD, 300 MHz): δ 1.14-1.48 (m, 10H), 2.28 (s, 2H), 2.99 (t, 2H, J = 6.0 Hz), 3.06 (t, 2H, J = 6.3Hz), 3.22 (s, 2H),

4.31 (t, 2H, J = 6.0 Hz), 4.46 (t, 2H, J = 6.3 Hz), 7.39-7.49 (m, 2H), 7.69-7.71 (m, IH). MS: (ES +) m/z 633.1 (M+H)⁺, 655.1 (M+Na)⁺.

Example 55

Synthesis of mutual prodrug of gabapentin ethyl ester and lamotrigine (I-AA-MPD12):

To a suspension of lamotrigine (2.70 g, 10.55 mmol) and DMAP (1.28 g, 10.55 mmol) in toluene (40 mL) at 110 °C was added a solution of the imidazolide of **I-A1-PD4** (4.99 g, 10.55 mmol) THF (20 mL) and stirred overnight at 110 °C. The reaction mixture was purified by column chromatography to afford 0.85 g (12 %) of **I-AA-MPD12** as a white solid. ¹ HNMR (CDCl₃, 300 MHz) δ 1.24 (t, 2H, J = 7.2 Hz), 1.36- 1.77 (m, 10H), 2.29 (s, 2H), 2.93-3.03 (m, 4H), 3.22 (d, 2H, J = 6.6 Hz), 4.11 (q, 2H, J = 7.2 Hz), 4.34 (t, 2H, J = 6.6 Hz), 4.47 (t, 2H, J = 6.3 Hz), 5.65 (t, IH), 7.34-7.41 (m, 2H), 7.60-7.63 (m, IH). MS: ES+ m/z 661 (M+H)+, 682 (M+Na)+.

Example 56

Synthesis of mutual prodrug of gabapentin ethyl ester and levetiracetam (I-AA-MPD13):

To a solution of levetiracetam (1.0 g, 5.87 mmol) in DCE (25 mL) and DCM (5 mL) at RT was added oxalyl chloride (895 mg, 7.05 mmol). The reaction mixture was refluxed for 8 h, after which it was cooled to RT and a solution of **I-A1-PD8** (2.67 g, 7.05 mmol) in DCE (20 mL) was added drop-wise. The resulting mixture was stirred at RT for 18 h. After usual aqueous work-up and chromatographic purification, 1.63 g (48%) of **I-AA-MPD13** was obtained as a yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 0.87 (t, 3H, J = 7.4 Hz), 1.25 (t, 3H, J = 7.1 Hz), 1.34-1.52 (m, 10H), 1.82-2.01 (m, 4H), 2.28 (s, 2H), 2.40 (t, 2H, J = 7.0 Hz), 2.89-2.94 (m, 4H), 3.04-3.11 (m, IH), 3.19 (d, 2H, J = 6.6 Hz), 3.66-3.75 (m, IH), 4.07-4.16 (m, 3H), 4.27-4.35 (m, 4H), 5.48 (t, IH, J = 6.5 Hz), 8.18 (bs, IH). MS: (ES+): m/z 576.1 [M+H]+; 598.1 [M+Naf. (ES-): m/z 574.2 [M-H]+.

25 Example 57

Synthesis of mutual prodrug of gabapentin ethyl ester and valproic acid (I-AA-MPD14): This mutual prodrug was synthesized according method outlined in Scheme 18. This mutual prodrug I-AA-MPD14 was obtained as oil. MS (m/z): 592 [M+H]⁺.

Example 58

30 Synthesis of mutual prodrug of gabapentin ethyl ester and valproic acid (I-AA-MPD15):

This mutual prodrug was synthesized according method outlined in Scheme 18. The mutual prodrug I-AA-MPD15 was obtained as a yellow oil. MS (m/z): 620 [M+H]⁺.

Example 59

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Synthesis of mutual prodrug of gabapentin ethyl ester and valproic acid (I-AA-MPD16): To a suspension of valpromide (750 mg, 5.24 mmol) in DCE (15 mL) at 0-5 0 C was added oxalyl chloride (0.5 mL, 6.29 mmol) and refluxed overnight. The reaction mixture was cooled to RT, treated with a solution of I-A1-PD8 (2.18 g, 5.76 mmol) in DCE (2 mL) and stirred at RT for 2 h. The reaction mixture was purified by column chromatography to afford 1.61 g (51%) of I-AA-MPD16 as a colorless oil. 1 H NMR (CDCl₃, 300 MHz): δ 0.89 (t, 6H, J = 7.09 Hz), 1.25 (t, 3H₅ J = 6.96 Hz), 1.31-1.69 (m, 18H), 2.29 (s, 3H), 2.89-2.99 (m, 4H), 3.20 (d, 2H, J = 6.47 Hz), 4.13 (q, 2H), 4.33 (t, 2H, J = 6.71 Hz), 4.40 (t, 2H, J = 5.97 Hz), 5.54 (t, IH), 8.29 (br s, IH). MS: ES+ m/z 549 [M+H]⁺, 571 [M+Na]⁺.

Example 60

15 Synthesis of double prodrug of valproic acid (I-AA-MPD22):

To a suspension of valpromide (3.0 g, 20.95 mmol) in DCE (30 mL) at 0-5 °C was added oxalyl chloride (1.3 mL, 15.08 mmol) and refluxed overnight. The reaction mixture was cooled to RT, a solution of SL-I (0.808 g, 5.24 mmol) in DCE (3 mL) was added and stirred overnight. After usual work-up and chromatographic purification, 1.97 g (43%) of I-AA-MPD22 were obtained as a white solid. ¹H NMR (CDCl₃, 300 MHz): δ 0.89 (t,

12H, J = 7.18 Hz), 1.28-1.66 (m, 16H), 2.94-2.95 (m, 2H), 3.02 (t, 6H, J = 6.51 Hz), 4.42 (t, 4H, J = 6.47 Hz). MS: m/z 493.2 [M+H] $^+$, 510.0 [M+NH₄] $^+$, 515.10 [M+Naf.

Example 61

Synthesis of mutual prodrug of gabapentin ethyl ester and valproic acid (I-AA-MPD27):

Step 1: To a solution of **I-A1-PD8** (4.0 g, 10.54 mmol) in THF (25 mL) was added CDI (2.22g, 13.7 mmol) and stirred at RT for 90 min. To this was added t-butyl carbazate (1.39 g, 10.54 mmol) and DMAP (1.288 g, 10.54 mmol), and stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 4.0 g (91%) of the intermediate boc-hydrazide was obtained as a colorless gummy material. ¹H NMR (CDCl₃, 300 MHz): δ 1.25 (t, 3H, J = 7.1 Hz), 1.43 (s, 9H), 1.31-1.74 (m, 10H), 2.30 (s,

2H), 2.90-3.01 (m, 4H), 3.20 (d, 2H, J = 6.6 Hz), 4.17 (q, 2H, J = 7.1 Hz), 4.32 (t, 2H, J = 6.5 Hz), 4.39 (t, 2H, J = 6.5 Hz), 5.42 (br s, IH), 6.04 (br s, IH), 6.98 (br s, IH).

Step 2: To a solution of the above boc-hydrazide (4.0 g, 7.44 mmol) in DCM (20 mL) was added 50% TFA/DCM (10 mL) and stirred at RT for Ih. DCM was removed under vacuum, the resulting residue triturated with diethyl ether (2 x 20 mL) and dried to give a colorless oil, which was dissolved in THF (20 mL). To the above solution at 0-5 0 C was added TEA (2.1 mL, 14.88 mmol), valproic acid (1.18 g, 8.184 mmol), DCC (2.3 g, 11.16 mmol) and DMAP (0.909 g, 7.44 mmol) and the mixture was stirred overnight at RT. The mixture was filtered, concentrated and purified by column chromatography to afford 2.59 g (51 %) of **I-AA-MPD27** as a colorless gummy material. 1 H NMR (CDCl₃, 300 MHz): δ 0.85 (t, 6H, **J** = 7.2 Hz), 1.3 (t, 6H, **J** = 7.11 Hz), 1.21-1.80 (m, 26H), 2.2-2.3 (m, IH), 2.35 (s, 2H), 2.81-2.94 (m, 4H), 3.21 (d, 2H, J = 6.6 Hz), 3.65-3.68 (m, IH), 4.19 (q, 2H, J = 7.11 Hz), 4.36 (t, 2H, J = 6.51 Hz), 4.39 (t, 2H, J = 6.51 Hz), 5.51 (t, IH), 8.17 (s, IH). MS: m/z 712 [M+Naf, 728 [M+K]⁺, 688 [M-H]⁻.

15 Example 62

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Synthesis of mutual prodrug of valproic acid and nicotinic acid (I-CC-MPD1):

Step 1: To a solution of nicotinyl chloride hydrochloride (3.16 g, 17.76 mmol) and **LI-2c** (3 g, 11.84 mmol) in THF (50 mL) was added TEA (8.3 mL, 59.2 mmol) and stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 4.14. g (97%) of LI-2c-nicotinate ester was obtained as a colorless oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.43 (s, 9H), 2.82 (t, 2H, J = 6.31 Hz), 3.42-3.48 (q, 2H), 4.62 (t, 2H, J = 6.59 Hz), 7.29-7.33 (m, 1H), 8.30 (d, 1H, J = 7.95 Hz), 8.78 (dd, 1H, J = 4.86, 1.72 Hz), 9.23 (d, 1H, J = 2.13 Hz). MS: m/z 358 [M+H]⁺, 381 [M+Naf, 739 [2M+Na]⁺.

Step 2: To a solution of LI-2c-nicotinate ester (0.92 g, 2.50 mmol) in DCM (5 mL) was added 50% TFA/DCM (5 mL) and stirred for Ih. Reaction mixture was concentrated and the residual TFA salt was used as such in Step 3.

Step 3: To a solution of valproic acid (0.37 g, 2.56 mmol) in THF (5 mL) was added CDI (0.5 g, 3.08 mmol) and stirred for 2h. This was treated with a solution of the above TFA salt, TEA (0.7 mL, 5.13 mmol) and DMAP (50 mg, 0.41 mmol) in THF (10 mL) and the mixture was stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 0.7 g (71%) of I-CC-MPD1 was obtained as a white solid. ¹H NMR

(CDCl₃, 500 MHz): δ 0.88 (t, 6H, J = 7 Hz), 1.25-1.59 (m, 8H), 2.06-2.08 (r α , IH), 2.86 (t, 2H, J = 6 Hz), 3.05 (t, 2H, J = 7 Hz), 3.58-3.61 (q, 2H, J = 9.0 Hz), 4.63 (t, 2H, J = 6.5 Hz), 7.40-7.42 (m, IH), 8.30 (dt, IH, J = 8.0, 2.0 Hz), 8.79 (dd, IH, J = 5.0, 2.0 Hz), 9.23 (d, IH, J = 0.5 Hz). MS: m/z 385 [M+H]⁺, 407 [M+Naf, 423 [M+K]⁺.

5 Example 63

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Synthesis of mutual prodrug of valproic acid and nicotinic acid (I-CC-MPD2):

This mutual prodrug was synthesized as described in Example 62, with obvious modifications. 0.612 g (41%) of **I-CC-MPD2** was obtained as a white solid. I H NMR (CDCl₃, 300 MHz): δ 0.89 (t, 6H, J = 7.23 Hz), 1.24-1.62 (m, 8H), 2.34-2.42 (m, IH),

2.92 (t, 2H, J = 6.83 Hz), 2.98 (t, 2H, J = 6.04 Hz), 3.78-3.84 (q, 2H), 4.37 (t, 2H, J = 6.79 Hz), 7.36-7.41 (m, IH), 8.15 (d, IH, J = 7.92 Hz), 8.73 (d, IH, J = 4.78 Hz), 9.02 (s, IH). MS: m/z 385 [M+H]⁺, 419 [MH-HCl]⁺, 383 [M-H]⁻.

Example 64

Synthesis of mutual prodrug of zidovudine and lamivudine (I-HH-MPD1):

15 Step 1: Synthesis of intermediate I-S17-PDI1:

4-Nitrophenyl chloroformate (0.27 g, 1.34 mmol) was added to a solution of the **I-HI-PD5** (0.4 g, 0.89 mmol) and pyridine (76 μ L, 1 mmol) in DCM (10 niL) and stirred at RT for 15 h. The mixture was concentrated and the residue purified by column chromatography to give 0.29 g (53%) of **I-S17-PDI1.** ^IH-NMR (300 MHz, CDCl₃): δ 1.93 (s, 3H), 2.45 (m, 2H), 2.97-3.06 (m, 4H), 4.05 (m, IH), 4.41 (m, IH), 4.40-4.49 (m, 4H), 4.54 (t, 2H, J = 6.5 Hz), 6.17 (t, IH, J = 6.0 Hz), 7.33 (s, IH), 7.39 (d, 2H, J = 4.8

Hz), 4.34 (t, 2H, J = 0.5 Hz), 0.17 (t, H1, J = 0.0 Hz), 7.35 (s, H1), 7.39 (d, 2H, J= 4.8 Hz) and 8.50 (s, IH). MS (m/z): 635 [M+Naf. Step 2: Synthesis of **I-HH-MPD1:** Lamivudine (45 mg, 0.196 mmol) and DMAP (48

mg, 0.39 mmol) were added to a solution of **I-S17-PDI1** (80 mg, 0.13 mmol) in DMF (1.5 mL) and stirred at RT for 30 min. The mixture was concentrated and purified by column chromatography to give 40 mg (43%) of product **I-HH-MPD1**. ^IH-NMR (300 MHz, CDCl₃): δ 1.90 (s, 3H), 2.45 (t, 2H, J = 6.1 Hz), 3.05 (t, 4H, J = 6.2 Hz), 3.20 (m, IH), 3.53 (m, IH), 4.08 (m, IH), 4.30-4.80 (m, 8H), 5.45 (t, IH, J = 3.0 Hz), 5.90 (d, IH, J = 7.5 Hz), 6.17 (t, IH), 6.30 (t, IH), 7.55 (s, IH) and 7.90 (d, IH, J = 7.50 Hz). MS

30 (m/z): 725 [M+Naf.

Synthesis of mutual prodrug of zidovudine and lamivudine (I-HH-MPD2b):

This mutual prodrug was synthesized according to the method outlined in Scheme 18. The mutual prodrug **I-HH-MPD2b** was obtained as a white solid. ^IH-NMR (300 MHz, CDCl₃): δ 1.97 (s, 3H), 2.42 (m, 2H), 2.90-2.94 (m, 16H), 3.06 (m, IH), 3.40-3.44 (m, 8H), 3.50-3.56 (m, IH), 3.71-3.73 (m, IH), 4.95 (m, IH), 4.27-4.30 (m, 4H), 4.37-4.49 (m, 4h), 5.32 (t, IH, J = 5.1 Hz), 5.83 (d, IH, J = 6.6 Hz), 6.07 (m, IH), 6.33 (bs, IH), 7.20-7.25 (m, IH), 7.74 (m, IH). MS (m/z): 954 [MH-Na]⁺.

Example 66

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10 Synthesis of mutual prodrug of cetirizine and pseudoephedrine (I-CA-MPD1):

Step 1: Synthesis of intermediate I-S17-PDI1:

This intermediate was prepared by reacting **I-C1-PD10** with p-nitrophenyl chloroformate by a procedure similar to that described in Example 64. The desired intermediate **I-S17-PD11** was obtained as a gum. 1 H-NMR (300 MHz, CDCl $_{3}$): δ 2.49-2.71 (m, 10H), 2.95 (t, 2H, J = 6.6Hz), 3.01 (t, 2H, J = 6.5 Hz), 3.73 (bs, 2H), 4.13 (s, 2H), 4.22 (s, IH), 4.41 (t, 2H, J = 6.6 Hz), 4.53 (t, 2H, J = 6.6 Hz), 7.18-7.40 (m, 11 H), 8.28 (d, 2H, J = 7.1 Hz). Step 2: The mutual prodrug **I-CA-MPD1** was synthesized by reacting intermediate **I-S17-PDI1** with pseudoephidrine by a procedure similar to that described in Example 64, Step 2. The desired mutual prodrug **I-CA-MPD1** was obtained as a colorless gummy ,material. 1 H-NMR (300 MHz, CDCl $_{3}$): δ 0.99-1.09 (d, 3H, J = 6.6 Hz), 2.45 (bs, 4H),

2.68 (bs, 6H), 2.90 (s, 3H), 2.91-2.94 (m, 4H), 3.71 (bs, 3H), 4.11 (s, 2H), 4.18 (s, IH),

Example 67

Synthesis of mutual prodrug of gabapentin ethyl ester and naproxen (I-CA-MPD5):

4.26-4.41 (m, 4H), 4.56 (m, 2H), 7.17-7.35 (m, 12H). MS (m/z): 716 [M+ H]⁺.

25 This mutual prodrug was synthesized by reacting **I-A1-PD8** and Naproxen using Scheme 11, Method B. This mutual prodrug was obtained as colorless oil. ^IH-NMR (300 MHz, CDCl₃): δ 1.25 (t, 3H, J = 7.1 Hz), 1.30-1.55 (m, 10H), 1.57 (d, 3H, J = 7.1 Hz), 2.27 (s, 2H), 2.84 (q, 4H, J = 6.4 Hz), 3.18 (d, 2H, J = 6.7 Hz), 3.80-3.88 (m, IH), 3.91 (s, 3H), 4.12 (q, 2H, J = 7.1 Hz), 4.20-4.40 (m, 4H), 5.35 (bt, IH), 7.05-7.20 (m, 2H), 7.39 (dd, 30 IH, J = 1.8 Hz, 8.4 Hz), 7.60-7.73 (m, 3H). MS (m/z): 592 [M+H]⁺, 614 [M+Na]⁺.

Synthesis of mutual prodrug of valproic acid and nicotinic acid (I-CA-MPD14):

This mutual prodrug .was synthesized using valpromide and nicotinyl chloride hydrochloride, according to the methods described in Scheme 13 and Scheme 17, with obvious modifications. 1.0 g of the mutual prodrug **I-CA-MPD14** was obtained as a yellow oil. 1 H NMR (CD₃OD, 300 MHz): δ 0.87 (t, 6H, J = 6 Hz), 1.26-1.75 (m, 9H), 2.83 (s, IH), 2.95-3.0 (m, 4H), 3.81 (t, 2H, J = 6 Hz), 4.44 (t, 2H, J = 6 Hz), 7.0 (s, IH), 7.4 (bs, IH), 7.42 (m, IH), 8.20 (d, IH), 8.65-8.74 (bs, 2H), 9.0 (s, IH). MS: ES⁺ m/z 428.1 [M+H]⁺, 450.1 [M+Naf.

10 Example 69

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Synthesis of mutual prodrug of valproic acid and nicotinic acid (I-CA-MPD15):

To a solution of **I-C1-PD13** (1.5 g, 4.63 mmol) and nicotinyl chloride hydrochloride (0.99 g, 5.56 mmol) in THF (25 mL) was added TEA (2 mL, 13.89 mmol) at 0 0 C and stirred for 20 h at RT. After usual aqueous work-up and chromatographic purification, 1.0 g (83%) of **I-CA-MPD15** was obtained as a yellow viscous liquid. 1 H NMR (CD₃OD, 500 MHz): δ 0.89 (t, 6H, J = 5.0 Hz), 1.29-1.33 (m, 8H), 1.64 (bs, 2H), 3 (t, 2H, **J**= 5.0 Hz), 3.07 (t, 2H, **J**= 5.0 Hz), 4.42 (t, 2H, **J**= 5.0 Hz), 4.63 (t, 2H, **J**= 5.0 Hz), 7.41-7.43 (m, IH), 8.31 (bs, IH), 8.78 (bs, IH), 9.26 (s, IH). MS: ES⁺ m/z 429 [M+H]⁺, 451[M+Na]⁺, 467 [M+K]⁺.

20 Example 70

Synthesis of mutual prodrug of gabapentin ethyl ester and nicotinic acid (I-CA-MPD18): To a solution of I-S12-PD2 (synthesized as described in Scheme 12, Method C) (3.76 g, 7.64 mmol) in THF (30 mL) was added nicotinyl chloride hydrochloride (1.5 g, 8.40 mmol), followed by TEA (4.26 mL, 30.56 mmol) and stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 0.87 g (23 %) of I-CA-MPD18 was obtained as a yellow oil. 1 H NMR (CDCl₃, 300 MHz): δ 1.24 (t, 3H, J = 6.0 Hz), 1.27-1.47 (m, 10H), 2.27 (s, 2H), 2.90-3.17 (m, 4H), 3.16 (d, 2H, J = 6.0 Hz), 3.79 (q, 2H, J = 6.0 Hz), 4.10 (q, 2H, J = 6.0 Hz), 4.36 (t, 2H, J = 6.0 Hz), 5.56 (bt, IH, J = 6.0 Hz), 7.32-7.38 (m, IH), 8.17(d, IH, J = 9.0 Hz), 8.71 (d, IH, J = 6.0 Hz), 9.07 (s, IH). MS: (ES)+ m/z 484 (M+H)+, 506 (M+Na)+; (ES)-m/z 482 (M-H)+.

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Synthesis of mutual prodrug of levetiracetam and valproic acid (I-CA-MPD19):

To a solution of levetiracetam (1.0 g, 5.87 mmol) in DCE (20mL) and DCM (4mL) was added oxalyl chloride (894 mg, 7.05 mmol) and heated at 80 $^{\circ}$ C for 7h. The reaction mixture was cooled to RT, a solution of I-C1-PD11 (1.97 g, 7.05 mmol) in DCE (10mL) was added and stirred at RT for 18 h. After usual aqueous work-up and chromatographic purification, 1.73 g (61 %) of I-CA-MPD19 was obtained as a yellow oil. 1 H NMR (CDC1₃, 300 MHz): δ 0.85-0.91 (m, 9H), 1.24-1.62 (m, 8H), 1.80-2.05 (m, 4H), 2.34-2.44 (m, 3H), 2.91 (t, 4H, J = 6.0 Hz), 3.03-3.12 (m, IH), 4.06-4.09 (m, IH), 4.31-4.36 (m, 4H), 8.32 (bs, IH). MS: (ES+) m/z 477.1 [M+H]+, 498.9 [M+Na]+ (ES)- m/z 475.0 [M-H]-.

Example 72

Synthesis of mutual prodrug of gabapentin ethyl ester and valproic acid (I-CA-MPD21): This mutual prodrug was synthesized by following a route depicted in Scheme 19, with obvious modifications. The mutual prodrug I-CA-MPD21 was obtained as a colorless oil. 1 H-NMR (CDCl₃, 300 MHz): δ 0.81 (t, 6H, J = 7.19 Hz), 1.15-1.60 (m, 21H), 2.20 (s, 2H), 2.25-2.35 (m, IH), 2.84 (t, 4H, J = 6.6 Hz), 3.11 (d, 2H, J = 6.7 Hz), 4.05 (q, 2H, J = 7.16 Hz and 17.3 Hz), 4.15-4.25 (m, 4H), 5.43 (bt, IH). MS (m/z): 506 [M+H]⁺, 528 [M+Na]⁺.

20 Example 73

Synthesis of mutual prodrug of gabapentin ethyl ester and nicotinic acid (I-CA-MPD22): To a suspension of nicotinyl chloride hydrochloride (0.35 g, 1.97 mmol) in THF (3 mL) at 0 $^{\circ}$ C was added TEA (0.82 mL, 5.91 mmol). After 5 min, a solution of I-A1-PD8 (0.5g, 1.31 mmol) and TEA (0.27 mL, 1.97 mmol) in THF (4 mL) was added and stirred overnight at RT. The mixture was purified by column chromatography to afford 0.573 g (90 %) of I-CA-MPD22 as a yellow oil. 1 H NMR (CDCl₃, 300 MHz): δ 1.24 (t, 3H, J = 6.0 Hz), 1.27-1.47 (m, 10H), 2.27 (s, 2H), 2.94 (t, 2H, J = 6.0 Hz), 3.07 (t, 2H, J = 6.0 Hz), 3.19 (d, 2H, J = 6.0 Hz), 4.12 (q, 2H, J = 6.0 Hz), 4.32 (t, 2H, J = 6.0 Hz), 4.62 (t, 2H, J = 6.0 Hz), 5.29 (bs, IH), 7.36-7.42 (m, IH), 8.30 (t, IH, J = 3.0 Hz), 8.78 (dd, IH, J = 1.69 Hz), 9.24(s, IH). MS: (ES)+m/z 485 (M+H)+, 507 (M+Na)+.

Synthesis of mutual prodrug of lamotrigine and valproic acid (I-CA-MPD23): To a suspension of lamotrigine (0.455 g, 1.78 mmol) and DMAP (0.217 g, 1.78 mmol) in toluene (10 mL) at $110~^{0}$ C was added a solution of the imidazolide of I-Cl-PDII (0.665 g, 1.78 mmol) in THF (5 mL). The reaction was stirred at $110~^{0}$ C overnight and purified by column chromatography to afford 0.20 g (20%) of I-CA-MPD23 as a white solid. 1 H NMR (300 MHz, CDCl₃): δ 0.86-0.90 (m, 6H), 1.20-1.44 (m, 6H), 1.53-1.62 (m, 2H), 2.36-2.39 (m, IH), 2.90-3.0 (m, 4H), 4.34 (t, 2H, J = 6.3 Hz), 4.46 (t, 2H J = 6.6 Hz), 7.36-7.38 (m, 2H), 7.60-7.63 (m, IH). MS: (ES +) m/z 562 (M+H)+, 585 (M +Na)+.

10 Example 75

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Synthesis of mutual prodrug of lamotrigine and nicotinic acid (I-CA-MPD24):

A solution of I-A1-PD4 (0.5 g, 1.14 mmol) and TEA (0.5 mL, 2.87 mmol) in THF (5 mL) was added to a suspension of nicotinyl chloride (0.305 g, 1.71 mmol) and 0.5 mL TEA in THF (5 mL). The mixture was stirred at RT for 24 h. After usual aqueous workup and chromatographic purification, 0.15 g (14%) of I-CA-MPD24 were obtained as a white solid. 1 HNMR (CDCl₃, 500MHz): δ 3.06 (t, 2H, J = 6.5Hz), 3.10 (t, 2H, J = 6.5 Hz), 4.49 (t, 2H, J = 6.5 Hz), 4.65 (t, 2H, J = 6.5 Hz), 7.38-7.43 (m, 3H), 7.60-7.62 (m, IH), 8.33-8.36 (m, IH), 8.81 (m, IH), 9.35 (bs, IH). MS: (ES +) m/z 540.9 (M+H)⁺. Example 76

- 20 Synthesis of mutual prodrug of lamotrigine and nicotinic acid (I-CA-MPD25):
- This mutual prodrug was synthesized using lamotrigine and nicotinyl chloride hydrochloride, according to the methods outlined in Scheme 12 and Scheme 17. 0.8 g (44%) of I-CA-MPD25.HC1 were obtained as an off white solid. 1 H NMR (D₂O, 500MHz): δ 2.93 (t, 2H, J = 6.5 Hz), 3.10 (t, 2H, J = 6.0Hz), 3.69 (t, 2H, J = 6.5Hz), 4.49
- 25 (m, 2H), 7.37-7.43 (m, 3H), 7.69-7.71 (m, IH), 8.05-8.07 (m, IH), 8.78-8.79 (m, IH), 9.30 (bs, IH). MS: (ES +) m/z 539.9 (MH-H)⁺, 561.8 (M +Na)⁺.

Example 77

Synthesis of mutual prodrug of metronidazole and norfloxacin (I-AH-MPDI): Step 1: Synthesis of imidazolide of I-H1-PD1:

CDI (319 mg, 1.97 mmol) was added to a solution of I-H1-PD1 (577 mg, 1.64 mmol) in DMF (8 mL) and stirred at RT for 4 h. The mixture was concentrated and the residue

purified by column chromatography to give 395 mg (54%) of the imidazolide of I-Hl-PDI. ¹H-NMR (300 MHz, CDCl₃): δ 2.50 (s, 3H), 2.92 (t, 2H, J = 6.0 Hz), 3.00-3.10 (m, 2H), 4.36 (t, 2H, J = 3.0 Hz), 4.47-4.51 (m, 2H), 4.57-4.70 (m, 4H), 7.07 (s, IH), 7.43 (s, IH), 7.95 (s, IH), 8.15 (s, IH). MS (m/z): 446 [M+H]⁺.

Step 2: Synthesis of I-AH-MPD1: A solution of the imidazolide of I-H1-PD1 (100 mg, 0.224 mmol) in DMF (1 mL) was added to a suspension of norfloxacin (86 mg, 0.269 mmol) in DMF (2 mL) and stirred at RT for 60 h. The mixture was concentrated and the residue purified by column chromatography to give 35 mg (22%) of I-AH-MPDI. ¹H-NMR (300 MHz, CDCl₃): δ 1.59 (t, 3H, J = 7.5 Hz), 2.53 (s, 3H), 2.86-2.97 (m, 4H), 3.27-3.30 (m, 4H), 3.72 (t, 4H, J = 4.5 Hz), 4.32-4.40 (m, 6H), 4.48-4.52 (m, 2H), 4.59-4.63 (m, 2H), 6.85 (d, IH, J = 6.0 Hz), 7.96 (s, IH), 8.09 (d, IH, J = 12.0 Hz), 8.68 (s, IH). MS (m/z): 697 [M+H]+.

The following mutual prodrugs (Examples 78 - 80) were obtained according to procedures similar to those described in Example 77, with the substitution of the appropriate pairs of amino-containing and hydroxyl-containing therapeutic agents:

Example 78

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Synthesis of mutual prodrug of metronidazole and norfloxacin (I-AH-MPD3b): The mutual prodrug I-AH-MPD3b was obtained as a yellow solid. 1 H-NMR (300MHz, CDCl₃): δ 1.59 (t, 3H, J = 7.1 Hz), 2.49 (s, 3H), 2.82-2.98 (m, 10H), 3.30 (t, 4H, J = 4.5 Hz), 3.39 (bs, 4H), 3.72 (t, 4H, J = 4.8 Hz), 4.38 (dt, 8H, J = 26.2, 6.4 Hz), 4.61 (t, 2H, J = 4.8 Hz), 6.86 (d, IH, J = 6.4 Hz), 7.95 (s, IH), 8.07 (bd, IH, J = 12.8 Hz), 8.67 (s, IH), 14.9 (s, IH). MS (m/z): 811.26 [M+H]⁺.

Example 79

Synthesis of mutual prodrug of gabapentin and tramadol (I-AH-MPD7):

The mutual prodrug was synthesized according to the method in Scheme 15 with obvious modifications. The mutual prodrug I-AH-MPD7 was obtained as a colorless gummy material. ¹H-NMR (300 MHz, CDCl₃): δ 1.25 (t, 3H, J = 7.1 Hz), 1.32-2.45 (m, 30H), 2.91-2.99 (m, 4H), 3.16 (t, 2H, J = 7.3 Hz), 3.80 (s, 3H), 4.08-4.15 (q, 2H, J = 7.1 Hz), 4.28-4.40 (m, 4H), 5.4 (t, IH), 6.74-6.81 (m, 3H), 7.23-7.29 (t, IH, J = 8 Hz). MS (m/z): 669.30 [M+H]⁺.

Example 80

Synthesis of mutual prodrug of venlafaxine and paroxetine (I-AH-MPD8)

The mutual prodrug was synthesized according to the method outlined in Scheme 15 with obvious modifications. The mutual prodrug **I-AH-MPD8** was obtained as a white sticky solid. ¹H-NMR was consistent with the expected structure. MS: m/z 812 [M]⁺.

5 Example 81

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Synthesis of NO-releasing prodrug of Valproic acid (I-C1-NOPD1):

This prodrug was synthesized as shown in Scheme 11, Method B using as reagents valproic acid (725 mg, 5.03 mmol), **LI-2b** (1 g, 5.03 mmol), TEA (611 mg, 6.04 mmol), DCC (1.25 g, 6.04 mmol) and DMAP (100 mg). Yield: 832 mg (51%). ¹H-NMR (300 MHz, CDCl₃): δ 0.89 (t, 6H, J = 7.09 Hz), 1.22-1.77 (m, 8H), 2.36-2.40 (m, IH), 2.93-3.00 (m, 4H), 4.34 (t, 2H, J = 6.8 Hz), 4.70 (t, 2H, J = 6.35 Hz). MS (CI)⁺ m/z: 326 [M+H]⁺.

Example 82

Synthesis of NO-releasing prodrug of valproic acid (I-Cl-NOPD3a):

This prodrug was prepared as shown in Scheme 13, Method A. Thus, to a stirred mixture of valproyl isocyanate, which was freshly prepared from valpromide (0.7 g, 4.90 mmol [valpromide was synthesized from valproic acid by using known methods as shown in Scheme 11, Method I) using a known method (see *J. Org. Chem.*, 1962, 27, 3742) in DCM (20 mL) at RT was added a solution of LI-2b (0.976 g, 4.90 mmol) in DCM (5 mL) drop-wise and stirred at RT for 2 h. The mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, afforded 0.6 g (33%) of prodrug I-Cl-NOPD3a. ¹H-NMR data is consistent with the expected structure. MS: [ES]+ m/z 391 [M+Na]+, 407.2 [M+K]+; [EI]+ m/z 368 [M + H]+.

Example 83

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25 Synthesis of NO-releasing prodrug of aspirin (I-C1-NOPD4):

This prodrug was synthesized as shown in Scheme 11, Method D. Thus, to a solution of aspirin (3.0 g, 16.65 mmol) in THF (30 mL) at 0 °C was added oxalyl chloride (1.86 mL, 21.64 mmol) and heated at 70 °C for 2 h. The mixture was concentrated, the residue was dissolved in THF (30 mL) and treated with a solution of L1-2a (3.61 g, 16.65 mmol), TEA (3.48 mL, 24.97 mmol) and DMAP (361 mg) in THF (20 mL). The resulting mixture was stirred at RT for 2 h and filtered through celite. The filtrate was concentrated

and the residue purified by column chromatography to afford 3.06 g (48%) of the bromide SII-II. ¹H-NMR (300 MHz, CDCl₃): δ 2.35 (s, 3H), 3.01-3.12 (m, 4H), 3.61 (t, 2H, J = 6.5 Hz), 4.53 (t, 2H, J = 6.0 Hz), 7.11 (dd, IH, J = 8 Hz, 1 Hz), 7.32 (t, IH, J = 7.6 Hz), 7.57 (t, IH, J = 7.6 Hz), 8.03 (dd, IH, J = 7.8 Hz, 1.6 Hz). MS (ES⁺) m/z: 403.92 (M+Na)⁺.

To a solution of **SII-II** (2.0 g, 5.27 mmol) in acetonitrile (20 mL) at 0 0 C was added AgNO₃ (1.07 g, 6.32 mmol) in the dark. The mixture was stirred at RT for 1.5 h, filtered through celite and concentrated. The residue, after usual aqueous work-up and chromatographic purification, afforded 0.965 g (50%) pure **I-C1-NOPD4**. 1 H-NMR (300 MHz, CDCl₃): δ 2.36 (s, 3H), 2.98 (t, 2H, J = 6.8 Hz), 3.05 (t, 2H, J = 6.4 Hz), 4.54 (t, 2H, **J** = 6.4 Hz), 4.70 (t, 2H, J = 6.8 Hz), 7.12 (d, IH, J = 8 Hz), 7.33 (t, IH, J = 7.6 Hz), 7.59 (t, IH, J = 7.5 Hz), 8.03 (dd, IH, J = 7.8 Hz, 1 Hz). MS (ES)⁺ m/z: 379.11 (M+NH₄)⁺, 383.98 (M+Na)⁺.

Example 84

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15 Synthesis of NO-releasing prodrug of aspirin (I-Cl-NOPD5a):

As shown in Scheme 11, Method H, this prodrug was synthesized in three steps:

Step 1: To a suspension of aspirin (1 g, 5.55 mmol) in benzene (15 mL) and DMF (1 drop) at 0-5 0 C was added a solution of oxalyl chloride (0.6 mL, 6.66 mmol) in benzene (5 mL) and stirred at 85 0 C for 2 h. The reaction mixture was concentrated, and the crude acid chloride was used immediately in the next step.

Step 2: To a solution of the above acid chloride in benzene (30 mL) was added silver cyanate (998 mg, 6.66 mmol) and refluxed in the dark for 1 h. The mixture, containing 2-acetoxybenzoyl isocyanate, was cooled to RT and used in the next step.

Step 3: To the above mixture was added a solution of **LI-2b** (1.33 g, 6.66 mmol) in benzene (5 mL) and stirred at RT for Ih. The mixture was filtered through celite and concentrated, and the residue was purified by column chromatography to afford 1.2 g (54%) of pure I-Cl-NOPD5a. ¹H-NMR data is consistent with the expected structure. MS (ES+) m/z: 404.98 [M+H]+, 426.94 [M+Na]+, 442.97 [M+K]+, (ES-) m/z: 403.01 [M-H]-.

30 Example 85

Synthesis of sodium salt of NO-releasing prodrug of aspirin (I-Cl-NOPD5b):

To a suspension of 60% sodium hydride (45 mg, 1.3 mmol) in THF (0.5 niL) was added solution of **I-CI-NOPD5a** (500 mg, 1.24 mmol) in THF (1.5 mL). After stirring for 5 min, THF was removed under vacuum, the residue was washed with dry Et₂O (4 x 3 mL) to remove unreacted starting material and dried in vacuum to afford 410 mg (78%) of **I-CI-NOPDSb** as an off-white solid. ¹H NMR (D₂O, 500 MHz): δ 2.28 (s, 3H), 2.93-2.97 (m, 4H), 4.33 (t, 2H, J = 6.0 Hz), 4.68 (t, 2H, J = 7.2 Hz), 7.07 (d, IH, J = 8.0 Hz), 7.26 (t, IH, J = 7.5 Hz), 7.41 (t, IH, J = 9.0 Hz), 7.57 (d, IH, J = 7.5 Hz). MS: m/z 427.0 [M+H]⁺, 449.0 [M+Na]⁺.

Example 86

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10 Synthesis of NO-releasing prodrug of aspirin (I-C1-NOPD6):

This prodrug was synthesized as shown in Scheme 11, Method E. Thus, to a solution of aspirin (1.20g, 6.70 mmol) in DCM (15 mL) at 0 0 C was added oxalyl chloride (0.74 mL, 8.65 mmol) and stirred at RT for 1.5 h. The mixture was concentrated and the residual acid chloride was treated with **LI-5.TFA** (6.70 mmol) in DCM (14 mL), followed by drop-wise addition of TEA (3.73 mL, 26.81 mmol) at 0 0 C. The mixture was stirred at RT for 4 h and concentrated. The residue, after usual aqueous work-up and chromatographic purification, gave 0.822g (34 %) of **I-C1-NOPD6.** 1 H-NMR (300 MHz, CDCl₃): δ 2.35 (s, 3H), 2.92 (t, 2H, J = 6.1 1 Hz), 2.98 (t, 2H, J = 6.0Hz), 3.76 (q, 2H, J = 6.0 Hz), 4.71 (t, 2H, J = 6.0 Hz), 6.70 (bs, IH), 7.10 (d, IH, J = 9.0 Hz), 7.31-7.33 (m, IH), 7.48-7.50 (m, IH), 7.78 (d, IH, J = 6.0 Hz). MS (EI)+ m/z: 361 (M+H)+.

Example 87

Synthesis of NO-releasing prodrug of nicotinic acid (I-C1-NOPD7):

This prodrug was synthesized as shown in Scheme 11, Method C. Thus, to a suspension of nicotinyl chloride hydrochloride (2.68 g, 15.07 mmol) in THF (10 mL) at 0 0 C was added a solution of **LI-2b** (2.0g, 10.05 mmol) and TEA (5.6 mL, 40.2 mmol) in THF (7 mL) and stirred at RT for 15 h. The mixture was filtered, concentrated and the residue purified by column chromatography to afford 2.23 g (73%) of pure **I-C1-NOPD7.** 1 H-NMR (300 MHz, CDCl₃): δ 3.01 (t, 2H, J = 4.75 Hz), 3.09 (t, 2H, J = 6.5 Hz), 4.63 (t, 2H, J = 5.25 Hz), 4.70 (t, 2H, J = 4.75 Hz), 7.39 - 7.42 (m, IH), 8.29-8.31 (dt, IH, J = 8 Hz, 2 Hz), 8.78-8.80 (dd, IH, J = 2 Hz), 9.23 (d, IH, J = 2Hz). MS (ES)⁺ m/z: 305 (M+H)⁺

Example 88

Synthesis of NO-releasing prodrug of nicotinamide (I-Cl-NOPD8a):

This prodrug was synthesized from nicotinamide (1 g, 8.18 mmol) according to the procedure described in Example 77 (see Scheme 11, Method I or Scheme 13, Method A). After usual workup, the crude product was purified by column chromatography to afford 0.1 g (3.5%) of prodrug I-Cl-NOPD8a. 1 H-NMR (300 MHz, CDCl₃): δ 2.97-3.0 (m, 4H), 4.51 (t, 2H, J = 6.3 Hz), 4.73 (t, 2H, J = 6.7 Hz), 7.38-7.48 (m, IH), 8.16-8.22 (m, IH), 8.71-8.79 (m, 2H), 9.04 (s, IH). MS [ES] $^{+}$ m/z: 348 [M+H] $^{+}$, 370 [M+Naf.

Example 89

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10 Synthesis of NO-releasing prodrug of nicotinic acid (I-C1-NOPD9):

This prodrug was synthesized as shown in Scheme 11, Method F. Thus, TEA (6.92 niL, 50.55 mmol) was added to a suspension of nicotinyl chloride hydrochloride (3.0 g, 16.85 mmol) and cysteamine hydrochloride (2.1 l g, 18.53 mmol) in DCM (30 niL) at 0 °C and stirred at RT for 4 h. The mixture was concentrated and the residue dissolved in MeOH (20 niL). To this solution at 0 °C was added a solution of LI-3b (4.1 l g, 16.85 mmol) in MeOH (5 mL), followed by TEA (4.61 mL, 33.70 mmol) and stirred overnight at RT. The mixture was filtered through celite, concentrated and the residue was purified by column chromatography to afford 3 g (58%) of pure I-C1-NOPD9.

1H-NMR (300 MHz, DMSO-d₆): 2.94 (t, 2H, J = 6.7 Hz), 3.09 (t, 2H, J = 6.3 Hz), 3.56 (q, 2H, J = 6.3 Hz), 4.73 (t, 2H, J = 6.3 Hz), 7.49-7.53 (m,IH), 8.16-8.19 (m, IH), 8.69-8.70 (m, IH), 8.87 (br

Example 90

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Synthesis of NO-releasing prodrug of naproxen (I-C1-NOPD10):

t, IH), 8.98 (s,IH). MS (ES⁺) m/z: 304 (M+H)⁺, 326 (M+Na)⁺.

This prodrug was synthesized as shown in Scheme 11, Method B. Thus, to a solution of naproxen (2.23 g, 9.7 mmol) and LI-2b (1.93 g, 9.7 mmol) in THF (70 mL) at RT were added DCC (3 g, 14.55 mmol) and DMAP (1.78 g, 14.55 mmol) and stirred overnight. The mixture was filtered and concentrated, and the residue purified by column chromatography to afford 1.03 g (25%) of pure I-C1-NOPD10. ¹H-NMR (300 MHz, CDCl₃): δ 1.59 (d, 3H, J = 7.16 Hz), 2.81 (t, 2H, J = 6.77 Hz), 2.87 (t, 2H, J = 6.42 Hz), 3.85-3.88 (m, IH), 3.91 (s, 3H), 4.33 (t, 2H, J = 5.26 Hz), 4.53 (t, 2H, J = 6.79 Hz), 7.10-7.16 (m, 2H), 7.41 (d, IH, J = 1.7Hz), 7.69 (t, 3H, J = 8.55 Hz).

Example 91

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Synthesis of NO-releasing prodrug of naproxen (I-C1-NOPD12):

This prodrug was synthesized as shown in Scheme 11, Method E. Thus, to a solution of naproxen (1.698 g, 7.37 mmol) in chloroform (20 mL) at 0-5 °C was added oxalyl chloride (0.8 mL, 8.844 mmol), followed by 2-3 drops of DMF. The mixture was stirred at RT for 90 min and concentrated. This acid chloride (~7.37 mmol) was treated with LI-5.TFA (6.7 mmol) in THF (20 mL) and cooled to 0 °C. To this was added TEA (5.6 mL, 40 mmol) and stirred at RT for 3 h. The mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, afforded 0.409 g (14%) of pure I-C1-NOPD12. ¹H-NMR (CDCl₃, 300 MHz): δ 1.24 (d, 3H), 2.87 (t, 2H, J = 6.5 Hz), 2.93 (t, 2H, J = 6.7 Hz), 3.64 (q, 2H, 7.5 Hz), 3.76 (m, IH), 3.88 (s, 3H), 4.70 (t, 2H, J = 6.6 Hz), 4.79 (br s, IH), 6.97-7.08 (m, 3H), 7.35-7.46 (m, 3H).

Example 92

15 Synthesis of NO-releasing prodrug of flurbiprofen (I-C1-NOPD13):

This prodrug was synthesized as shown in Scheme 11, Method A, using as reagents flurbiprofen (4.0 g, 16.37 mmol), CDI (3.97 g, 24.56 mmol) and **LI-2b** (3.25 g, 16.37 mmol). Yield: 3 g (43%). 1 H-NMR (300 MHz, CDCl₃): δ 1.56 (d, 3H, J = 7.2 Hz), 2.80-3.0 (m, 4H, J = 5.67 Hz), 3.78 (q, IH, **J** = 7.10 Hz), 4.36 (m, 2H), 4.66 (t, 2H, J = 6.78), 7.11-7.54 (m, 8H).

Example 93

Synthesis of NO-releasing prodrug of flurbiprofen (I-Cl-NOPD14a):

This prodrug was synthesized as shown in Scheme 11, Method I. Thus, to a solution of flurbiprofen (5.0 g, 20.46 mmol) in benzene (50 mL), was added oxalyl chloride (3.11 g, 24.55 mmol) at 0 °C and 2 drops of DMF and stirred at RT for 20 hrs. Benzene was removed under vacuum and the residue was diluted with DCM (50mL). The reaction mixture was cooled to 0 °C and dry ammonia was passed for 30 min. The reaction mixture was concentrated and, after usual aqueous work-up, 4.5 g of flurbiprofen amide was obtained as a white solid.

To a solution of flurbiprofen amide (3.0 g, 12.33 mmol) in DCM (70 mL) was added oxalyl chloride (1.87g, 14.79mmol) at 0 °C and refluxed for 16 h. Reaction mixture

was cooled to RT and treated with **LI-2b** (2.45 g, 12.33 mmol) in DCE (10mL) and stirred overnight. After usual aqueous work-up and chromatographic purification, 0.5 g of **I-Cl-NOPD14a** were obtained. ¹H NMR (CDCI₃, 300 MHz): δ 1.55 (d, 3H, J = 6.9 Hz), 2.94-2.97 (bs, 4H), 4.38-4.47 (bs, 3H), 4.68 (t, 2H, J = 6.6 Hz), 7.13-7.55 (bs, 8H) MS: ES⁺ m/z 469.03 [M+H]⁺, 467. 16 [M-H]⁺.

Example 94

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Synthesis of NO-releasing prodrug of flurbiprofen (I-Cl-NOPD15b):

This prodrug was synthesized as shown in Scheme 11, Method A. Thus, to a solution of flurbiprofen (2.5 g, 10.23 mmol) in THF (30 mL) was added CDI (3.31 g, 20.46 mmol) and stirred at RT for 16 h. To this was added LI-5.TFA (3.64 g, 10.23 mmol) in THF (15 mL), followed by TEA (2.85 mL, 20.46 mmol) and stirred for 16 h. After usual work-up and chromatographic purification, 1.5 g (91%) of I-Cl-NOPD15b were obtained. 1 H NMR (CDCI₃, 300 MHz): δ 1.5 (d, 3H, J = 6.9 Hz), 2.82 (t, 2H, J = 6.3 Hz), 2.92 (t, 2H, J = 6.9 Hz), 3.50 (m, 3H), 4.6 (t, 2H, J = 6.6 Hz), 5.8 (s, IH), 7.11-7.55 (bs, 8H). MS: ES⁺ m/z 425.21 [M+H]⁺, 423.11 [M-H]⁺.

Example 95

Synthesis of NO-releasing prodrug of indomethacin (I-C1-NOPD16):

This prodrug was synthesized as shown in Scheme 11, Method A. Thus, to a solution of indomethacin (2.0 g, 5.59 mmol) in chloroform (25 mL) was added CDI (1.09 g, 6.71 mmol) and stirred for 2h. A solution of LI-2b (1.22 g, 6.15 mmol) and DMAP (751 mg, 6.15 mmol) in chloroform (5 mL) was added, and the mixture was stirred at RT for 16 h. After usual aqueous work-up and chromatographic purification, 2.02 g (67%) of pure I-C1-NOPD16 was obtained. ¹H-NMR (300 MHz, CDCl₃): δ 2.39 (s, 3H), 2.88-2.95 (m, 4H), 3.69 (s, 2H), 3.84 (s, 3H), 4.38 (t, 2H, J = 6.3 Hz), 4.63 (t, 2H, J = 6.6 Hz), 6.67 (dd, IH, J = 2.4, 8.7 Hz), 6.87 (d, IH, J = 8.7 Hz), 6.96 (d, IH, J = 2.1 Hz), 7.47 (d, 2H, J = 8.4 Hz), 7.67 (d, 2H, J = 8.4 Hz). MS (ES⁺) m/z: 539.2 [M+H]⁺, 560.79 [M+Na]⁺.

Example 96

Synthesis of NO-releasing prodrug of indomethacin (I-C1-NOPD18):

This prodrug was synthesized as shown in Scheme 11, Method A. Thus, to a solution of indomethacin (3.01 g, 8.42 mmol) in THF (50 mL) at RT was added CDI (1.64 g, 10.10 mmol). After 1 h, **LI-5.TFA** (3 g, 8.42 mmol) was added at 0 °C, followed by TEA (5.9

mL, 42.1 mmol) and DMAP (0.6 g, 4.91 mmol). The reaction mixture was stirred at RT for 2 d. After usual aqueous work-up and chromatographic purification, 3.16 g (70%) of **I-C1-NOPD18** were obtained as yellow solid. ¹H NMR (CDCl₃, 300 MHz): δ 2.38 (s, 3H), 2.79 (t, 2H, J = 6.3 Hz), 2.86 (t, 2H, J = 6.9 Hz), 3.54 (q, 2H, J = 6.0 Hz), 3.66 (s, 2H), 3.83 (s, 3H), 4.61 (t, 2H, J = 6.6 Hz), 6.01 (bs, IH), 6.71 (dd, IH, J = 2.1, 9.0 Hz), 6.9 (dd, 2H, J = 3.3, 8.1 Hz), 7.49 (d, 2H, J = 8.4 Hz, 2H), 7.66 (d, 2H, J = 8.4 Hz). MS: m/z 538.10 [M+H]⁺, 560.1 [M+Na]⁺.

Example 97

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Synthesis of NO-releasing prodrug of ketoprofen (I-C1-NOPD19):

This prodrug was synthesized as shown in Scheme 11, Method A according to the method described in Example 90, using as reagents ketoprofen (1.27 g, 5 mmol), CDI (1.21 g, 7.5 mmol) and LI-2b (1 g, 5 mmol). Yield: 0.6 g (51%). ¹H-NMR (300 MHz, CDCl₃): δ 1.55 (d, 3H, J = 7.0 Hz), 2.80-2.95 (m, 4H), 3.82 (q, IH, J = 6.7 Hz), 4.35 (t, 2H, J = 6.1 Hz), 4.64 (t, 2H, J = 6.5 Hz), 7.40-7.85 (m, 9H). MS (ES+) m/z: 436.06
[M+H]⁺, 458.02 [M+Na]⁺.

Example 98

Synthesis of NO-releasing prodrug of ketoprofen (I-Cl-NOPD20a):

This prodrug was synthesized as shown in Scheme 11, Method I. Thus, to a solution of the amide of ketoprofen (1.78 g, 7 mmol) in DCE (70 mL) was added oxalyl chloride (1.0 g, 8.4 mmol) at 0 °C and refiuxed for 16 h. After cooling to RT, a solution of LI-2B (1.4 g, 7 mmol) in DCE (10 mL) was added and stirred for 20 h. After usual aqueous work-up and chromatographic purification, 0.6 g (17 %) of I-Cl-NOPD20a was obtained as a pale yellow gum. ¹H NMR (CDCl₃, 300 MHz): δ 1.47 (d, 3H, J = 6.96 Hz), 3.00 (bs, 4H), 4.00 (q, IH, J = 6.81 Hz), 4.39 (t, 2H, J = 6.21 Hz), 4.68 (bs, 2H), 7.47-7.77 (bs, 9H).
MS: ES+ m/z 478[M+H]+, 477.15[M-H]+.

Example 99

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Synthesis of NO-releasing prodrug of diclofenac (I-C1-NOPD22):

This prodrug was synthesized as shown in Scheme 11, Method B, using as reagents diclofenac (1.0 g, 3.378 mmol), **LI-2b** (0.68 g, 3.37 mmol), DMF (8 mL), DCC (0.835 g, 4.054 mmol) and DMAP (0.082 g, 0.675 mmol). Yield: 0.35 g (22 %). ¹H-NMR (300 MHz, CDCl₃): δ 2.91-3.04 (m, 4H), 3.85 (s, 2H), 4.42 (t, 2H, J = 6.6 Hz), 4.72 (t, 2H, J =

6.6 Hz), 6.56 (d, IH, J= 8.1 Hz), 6.82 (s,lH), 6.94-7.03 (m, 2H), 7.12-7.27 (m,2H), 7.35 (d, IH, J= 8.1Hz). MS (ES⁺) m/z: 476.90 [M+H]⁺, 498.86 [M+Naf.

Example 100

Synthesis of NO-releasing prodrug of flurbiprofen (I-C1-NOPD26):

5 This prodrug was synthesized as outlined in Scheme 20. Thus, to a solution of S20-I1 (0.8 g, 2.90 mmol) in THF (10 mL) and DMF (10 mL) was added the cesium salt of flurbiprofen (1.2 g, 3.19 mmol) and stirred at RT for 2 h. After usual aqueous work-up and chromatographic purification, 1.13 g (80 %) of I-C1-NOPD26 was obtained as a light yellow semi solid. ¹H NMR (500 MHz, CDCl₃): δ 1.58 (d, 3H, J = 7.5 Hz), 2.88-10 2.94 (m, 4H), 3.88 (q, IH, J= 7.0 Hz), 4.40 (t, 2H, J = 6.5 Hz), 4.64-4.68 (m, 4H), 7.14-7.54 (m, 8H). MS: m/z 501.1 [M+NH₄]⁺, 506.1 [M+Naf.

Example 101

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Synthesis of NO-releasing prodrug of gabapentin ethyl ester (I-A1-NOPD1):

This prodrug was synthesized as shown in Scheme 12, Method A. Thus, to a stirred solution of diphosgene (0.88 mL, 7.37 mmol) in DCM (3 mL) at 0 °C was added dropwise a solution of LI-2a (0.80 g, 3.68 mmol) & Hunig's base (1.92 mL, 11.85 mmol) in DCM (1 mL). The mixture was stirred at 0 °C for 30 min and concentrated. The residue was dissolved in DCM (4 mL) and treated with gabapentin ethyl ester hydrochloride (0.95 g, 4.05 mmol) & Hunig's base (1.39 mL, 8.05 mmol). The mixture was stirred at RT for 3 h and concentrated. The residue, after usual aqueous work-up, gave 1.6 g (98 %) of I-S12-I1. ¹H-NMR data is consistent with the expected structure. MS (ES⁺) m/z: 444 [M+H]⁺, 465.9 [M+Na]⁺.

To a stirred solution of **I-S12-I1** (1.3 g, 2.94 mmol) in acetonitrile (8 mL) at RT was added silver nitrate (0.6 g, 3.52 mmol) portion-wise and stirred at RT for 2.5 h. After filtration through celite, the filtrate was concentrated and the residue purified by column chromatography to afford 0.561 g (45 %) of prodrug **I-A1-NOPD1.** ¹H-NMR data is consistent with the expected structure. MS (ES⁺) m/z: 425 (M+H)⁺, 447 (M+Na)⁺.

Example 102

Synthesis of NO-releasing prodrug of lamotrigine (I-Al-NOPD3a and I-Al-NOPD3b):

This prodrug was synthesized as shown in Scheme 12, Method B. Thus, to a suspension of lamotrigine (1 g, 3.90 mmol) in toluene (20 mL) at 120 °C was added drop-wise a

solution of the imidazolide of **LI-2b** (1.4 g, 4.70 mmol) in THF (10 mL) and refluxed for 6 h. After usual aqueous work-up and chromatographic purification, 340 mg (20%) of **I-AI-NOPD-3a/b** was obtained. ¹H-NMR data is consistent with the expected structure. MS (ES)+ m/z: 481 (M+H)+.

5 Example 103

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Synthesis of NO-releasing prodrug of nicotinic hydrazide (I-A1-NOPD4):

This prodrug was synthesized from nicotinic hydrazide (235 mg, 1.70 mmol) according to the procedure described in Example 109 (see Scheme 13, Method B). After usual workup, the crude product was purified by column chromatography to afford 0.21 g (34%) of prodrug I-A1-NOPD4. 1 H-NMR (300 MHz, DMSO-d₆): δ 3.02 (t, 2H, J = 5.8 Hz), 3.10 (t, 2H, J = 6.1 Hz), 4.28 (t, 2H, J = 5.8 Hz), 4.76 (t, 2H, J = 6.1 Hz), 7.51-7.55 (dd, IH, J = 4.8 Hz, 7.7 Hz), 8.17 (d, IH, J = 7.8 Hz), 8.74 (d, IH, J = 3.8 Hz), 8.98 (s, IH), 9.44 (bs, IH), 10.54 (bs, IH). MS (EI)+m/z: 363 [M+H]+.

Example 104

15 Synthesis of NO-releasing prodrug of lisinopril dimethyl ester (I-A1-NOPD5):

This prodrug was synthesized from lisinopril dimethyl ester hydrochloride (1.10 g, 2.56 mmol) according to the procedure described in Example 101 (see Scheme 12, Method B). After usual workup, the crude product was purified by column chromatography to afford 0.76 g (67%) of prodrug **I-A1-NOPD5.** ¹H-NMR (300 MHz, CDCl₃): δ 1.49-1.54 (m, 2H), 1.93-2.07 (m, 8H), 2.12-2.28 (m, IH), 2.64-2.68 (m, 2H), 2.91-3.0 (m, 4H), 3.18-3.25 (m, 3H), 3.42-3.47 (m, IH), 3.52-3.55 (m, 2H), 3.69 (s, 3H), 3.73 (s, 3H), 4.28 (t, J = 6.3 Hz, 2H), 4.47-5.05 (m, IH), 4.69 (t, J = 6.8 Hz, 2H), 5.22 (bt, IH), 7.14-7.19 (m, 3H), 7.23-7.28 (m, 2H). MS (EI)+m/z: 659 [M+H]+.

Example 105

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25 Synthesis of NO-releasing prodrug of omeprazole (I-A1-NOPD6):

This prodrug was synthesized as shown in Scheme 12, Method B. To an ice-cold solution of diphosgene (0.3 mL, 2.48 mmol) in toluene at 0 °C, was added a mixture of **LI-2b** (0.5 g, 2.51 mmol) and TEA (0.42 mL, 3.0 mmol) in toluene (3 mL) and stirred for 2 h. In a separate flask, omeprazole (0.867 g, 2.50 mmol) was dissolved in THF (5 mL), cooled to 0 °C and NaH (0.059 g, 2.5 mmol) was added. The mixture was stirred for 30 min, the above reaction mixture was added dropwise to it and stirred for 2 h. After usual aqueous

work-up and chromatographic purification, 0.23 g (20 %) of **I-A1-NOPD6** was obtained as a reddish-yellow gum. ¹H-NMR: (CDCl₃, 300 MHz): 2.21 (s, 3H), 2.36 (s, 3H), 2.93-3.05 (m, 2H), 3.19-3.28 (m, 2H), 3.88 (s, 3H), 3.92 (s, 3H), 4.70-4.87 (m, 6H), 7.10-7.80 (m, 3H), 8.10 (s, IH). MS: ES+ m/z 571 (M+H)+, 593 (M+Na)+.

5 Example 106

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Synthesis of NO-releasing prodrug of hydralazine (I-A1-NOPD7):

This prodrug was synthesized from hydralazine hydrochloride (0.99g, 5.01mmol) according to the procedure described in Example 109 (see Scheme 13, Method B). After usual workup, the crude product was purified by column chromatography to afford 0.8 g (41%) of prodrug I-A1-NOPD7. ¹H-NMR (300 MHz, CDCl₃): δ 2.95-3.06 (m, 4H), 4.43 (t, 2H, J = 6.35Hz), 4.69 (t, 2H, J = 6.7 Hz), 7.57 (m, IH), 7.63-7.71(m, 2H), 8.16 (s, IH), 8.29 (d, IH, J = 7.6 Hz). MS (ES⁺) m/z: 386.05 (M+H)⁺.

Example 107

Synthesis of NO-releasing prodrug of amlodipine (I-A1-NOPD8):

This prodrug was synthesized from amlodipine (1.67 g, 4.09 mmol) according to the procedure described in Example 109 (see Scheme 12, Method B). After usual workup, the crude product was purified by column chromatography to afford 1.33 g (61%) of **I-A1-NOPD8.** ¹H-NMR (300 MHz, CDCl₃): δ 1.18 (t, 3H, J = 7.1 Hz), 2.36 (s, 3H), 2.93-2.99 (m, 4H), 3.47 (bs, 2H), 3.61-3.64 (m, 5H), 4.04 (q, 2H, J = 7.1 Hz), 4.35 (bt, 2H), 4.68-4.74 (m, 4H), 5.0 (bs, IH), 7.13-7.36 (m, 4H). MS (ES⁺) m/z: 634.14 (M+H)⁺, 656.83 (M+Na)⁺; (ES̄) m/z: 631.94 (M-H)⁺.

Example 108

Synthesis of NO-releasing prodrug of levetiracetam (I-A2-NOPDla):

This prodrug was synthesized from levetiracetam (1.0 g, 5.87 mmol) according to the procedure generally described in Example 82 (see Scheme 13, Method A). After usual workup and chromatographic purification, the product was further purified by preparative HPLC to afford 728 mg (31%) of prodrug **I-A2-NOPDla.** ¹H-NMR was consistent with the expected structure. MS (ES)⁺ m/z: 396.1 [M+H]⁺, 418.1 [M+Na]⁺, (ES)⁻ m/z: 394.1 [M-H]⁻.

30 Example 109

Synthesis of NO-releasing prodrug of valdecoxib (I-A3-NOPDla):

This prodrug was synthesized as shown in Scheme 13, Method B. Thus, to a cold suspension of sodium hydride (271 mg, 6.81 mmol) in THF (7 mL) was added drop-wise a solution of valdecoxib (1.78 g, 5.68 mmol) in THF (15 mL) and stirred at RT for 2 h. A solution of the imidazolide of **LI-2b** (2.0 g, 6.81 mmol) in THF (15 mL) was added and stirred at room temperature for 18 h. The reaction mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, afforded 976 mg (32 %) of prodrug **I-A3-NOPDIa.** ¹H-NMR data is consistent with the expected structure. MS (ES) m/z: 538 [M-H].

Example 110

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10 Synthesis of NO-releasing prodrug of celecoxib (I-A3-NOPD2a):

This prodrug was synthesized from celecoxib (6.62 g, 17.35 mmol) according to the procedure described in Example 109 (see Scheme 13, Method B). After usual workup, the crude product was purified by column chromatography to afford 1.55 g (15%) of prodrug I-A3-NOPD2a. 1 H-NMR (300 MHz, CDCl₃): δ 2.38 (s, 3H), 2.84-2.98 (m, 4H), 4.34 (t, 2H, J = 6.45 Hz), 4.63-4.71 (m, 2H), 6.74 (s, IH), 7.09-7.25 (m, 4 H), 7.51 (d, 2H, J = 6.8 Hz), 8.02 (d, 2H, J = 6.8 Hz). MS (ES)+ m/z: 606.87 [M + H]+, 628.93 [M + Na]+; (ES)- m/z: 604.88 [M-H]-.

Example 111

Synthesis of NO-releasing prodrug of paracetamol (I-H1-NOPD1):

This prodrug was synthesized as shown in Scheme 14, Method B. Thus, to a solution of paracetamol (2.0 g, 13.24 mmol) in THF (20 mL) was added CDI (2.36 g, 14.57 mmol) and the mixture was stirred at RT for 3 h. To this was added a solution of LI-2b (1.21 g, 6.62 mmol), followed by DMAP (0.802 g, 6.622 mmol) and stirred overnight at RT. The mixture was quenched with water and extracted with EtOAc. After usual aqueous work-up and chromatographic purification, 0.3 g (6%) of prodrug I-H1-NOPD1. H-NMR data is consistent with the expected structure. MS (Cl)+ m/z: 376 [M+H]+.

Example 112

Synthesis of NO-releasing prodrug of paracetamol (I-HI-NOPD2a):

This prodrug was synthesized as shown in Scheme 14, Method D. Thus, to a solution of chlorocarbonyl isocyanate (0.701g, 6.622 mmol) in benzene (5 mL) at 0 °C was added a solution of paracetamol (1 g, 6.622 mmol) and stirred at 0 °C for 1 h. To this was added a

solution of LI-2b (1.21 g, 6.622 mmol) and TEA (1 mL) in THF (5 mL), and stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 90 mg (3%) of prodrug I-HI-NOPD2a was obtained. ¹H-NMR data was consistent with the expected structure. MS: (ES) m/z: 418 [M-H].

5 Example 113

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Synthesis of NO-releasing prodrug of paracetamol (I-H1-NOPD3):

This prodrug was synthesized from paracetamol (2.0 g, 13.24 mmol) according to the procedure described in Example 122 (see Scheme 14, Method C). After usual workup, the crude product was purified by column chromatography to afford 1.0 g (20%) of prodrug I-H1-NOPD3. 1 H-NMR (500 MHz, CDCl₃): δ 2.1 l (s, 3H), 2.91 (t, 2H, J = 6.5 Hz), 3.06 (t, 2H, J = 6.5 Hz), 3.49 (t, 2H, J = 6.5 Hz), 4.75 (t, 2H, J = 6.5 Hz), 7.05 (d, 2H, J = 9.0 Hz), 7.54 (d, 2H, J = 9.0 Hz). MS (ES)⁺ m/z: 376 [M+H]⁺, 393 [M+NH₄]⁺, 397 [M+K]⁺.

Example 114

- 15 Synthesis of NO-releasing prodrug of metronidazole (I-H1-NOPD6):
 - This prodrug was synthesized in two steps as shown in Scheme 14, Method C.
 - Step 1: To a suspension of metronidazole (5 g, 29.22 mmol) in chloroform (100 mL) was added CDI (5.21 g, 32.2 mmol) and stirred overnight at RT. The reaction mixture, after usual aqueous work-up, gave 7.66 g (98 %) of the imidazolide intermediate. ¹H-NMR
- data was consistent with the expected structure. MS (ES)+ m/z: 266.1 [M + H]+.
 - Step 2: To a mixture of LI-5.TFA (2.68 mmol) and TEA (1.08 g, 10.72 mmol) in DCM (10 mL) at 0 °C was added the imidazolide of metronidazole (0.78 g, 2.95 mmol) and stirred at RT for 48 h. The reaction mixture was quenched with water and extracted with DCM. After usual aqueous work-up and chromatographic purification, 50 mg (4.3%) of
- 25 **I-H1-NOPD6** was obtained. ¹H-NMR (500 MHz, CDCl₃): δ 2.50 (s, 3H), 2.80 (t, 2H, J = 6.3 Hz), 2.96 (t, 2H, J = 6.6Hz), 3.47-3.50 (m, 2H), 4.41 (t, 2H, J = 5.1Hz), 4.58 (t, 2H, J = 5.1Hz), 4.70 (t, 2H, J = 6.6Hz), 7.96 (s, IH). MS (ES)⁺ m/z: 395.99 [M+H]⁺.

Example 115

Synthesis of NO-releasing prodrug of budesonide (I-H1-NOPD9):

30 This prodrug was synthesized from budesonide (0.5 g, 1.16 mmol) according to the procedure described in Example 122 (see Scheme 14, Method C). After usual workup,

the crude product was purified by column chromatography to afford 0.25 g (33%) of prodrug I-H1-NOPD9. 1H-NMR data was consistent with the expected structure. MS $(ES)^{+}$ m/z: 655 $[M+H]^{+}$.

Example 116

Synthesis of NO-releasing prodrug of 4-Hydroxy-TEMPO (I-H1-NOPD10): 5 A solution of L1-2b (0.20 g, 1.20 mmol) and CDI (0.195 g, 1.20 mmol) in chloroform (5 mL) was stirred at RT for 2 h, which was followed by the addition of 4-hydroxy-TEMPO (0.173 g, 1.00 mmol) and DMAP (0.122 g, 1.00 mmol). The mixture was refluxed for 2 d, then purified by column chromatography to afford 110 mg (27 %) of I-H1-NOPD10 as a red oil. MS: EI+ m/z 398 [M+H]+, 420 [MH-Na]+. 10

Example 117

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Synthesis of NO-releasing prodrug of edaravone (I-H1-NOPD11):

To a solution of edaravone (0.87 g, 5 mmol) in acetonitrile was added KF-Al₂O₃ (66 g) and, under thorough mixing, LI-3a (2.8 g, 10 mmol) was added. The mixture was agitated for 20 h. After usual aqueous work-up and chromatographic purification, 70 mg (4%) of the intermediate bromide was obtained as a reddish-yellow oil. IH NMR (CDCl $_3$, 500 MHz): δ 2.28 (s, 3H), 3.00-3.10 (m, 4H), 3.59 (t, 2H, J = 8 Hz), 4.34 (t, 2H, J = 6.5 Hz), 5.5 (s, IH), 7.4 (t, 2H, J = 1 Hz), 7.69 (t, 3H, J = 1 Hz). MS: ES⁺ m/z 375 [MH-H]⁺, 397.0 [MH-Na]⁺.

- To a solution of the above bromide (0.05 g, 0.134 mmol) in acetonitrile (1.5 mL) was 20 added AgNO 3 (0.027 g, 0.160 mmol) and stirred for 20 h. After usual aqueous workup and purification, 0.025 g (53 %) of I-H1-NOPD11 was obtained as a brown gum. 1H NMR (CDCl₃, 500 MHz): δ 2.28 (s, 3H), 2.90 (t, 2H, J = 6.5 Hz), 3.10 (t, 2H, J = 6.5 Hz), 4.33 (t, 2H, J = 6.0 Hz), 4.63 (t, 2H, J= 6.5 Hz), 5.5 (s, IH), 7.60-7.63 (bs, 2H), 7.65-7.67 (bs, 3H). MS: ES+ m/z 356 [MH-H]+.
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Biological Example 1:

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Screening of prodrugs and mutual prodrugs of anticonvulsants:

Most of the prodrugs and mutual prodrugs of anticonvulsants described in this invention were evaluated at National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Health (NIH), under their Antiepileptic Screening Program (ASP).

Test 1 is an initial screening for anticonvulsant activity in the Maximal Electroshock Test (MES) and Subcutaneous Metrazol Seizure Threshold Test (scMET) models combined with an initial assessment of toxicity (TOX) in mice via i.p. injection (see further explanation below). The data for each condition is presented as N/F, where N = number of animals protected from seizure and F = number of animals tested. For test of toxicity, N = number of animals displaying toxic effects and F = number of animals tested. Any deaths occurring during the test were recorded.

Maximal Electroshock Test (MES): The MES is a model for generalized tonic-clonic seizure and provides an indication of a compound's ability to prevent seizure spread when all neuronal circuits in the brain are maximally active. These seizures are highly reproducible and electro-physiologically consistent with human seizures. For all tests based on MES convulsions, 60 Hz of alternating current (50 mA in mice) is delivered for 2s by corneal electrodes, which have been primed with an electrolyte solution containing an anesthetic agent (0.5% tetracaine hydrochloride). Mice were tested at various intervals following doses of 30, 100 and 300 mg/kg of test compound given by i.p. injection of a volume of 0.01 mL/g. Other doses can be used if indicated by previously known pharmacology. An animal is considered "protected" from MES-induced seizures upon abolition of the hind-limb tonic extensor component of the seizure.

Subcutaneous Metrazol Seizure Threshold Test (scMET): Subcutaneous injection of the convulsant metrazol produces clonic seizures in laboratory animals. The scMET test detects the ability of the test compound to raise the seizure threshold of an animal and thus protect it from exhibiting a clonic seizure. Animals were pretreated with various doses of the test compound given by i.p. injection. At the previously determined

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Time to Peak Effect (TPE) of the test compound, the dose of metrazol which will produce convulsions in 97% of animals (CD 47: 85 mg/kg in mice) was injected into a loose fold of skin in the midline of the neck. The animals were placed in isolation cages to minimize stress and observed for the next 30 minutes for the presence or absence of a seizure. An episode of clonic spasms, approximately 305 seconds, of the fore and/or hind limbs, jaws, or vibrissae is taken as the end point. Animals which do not meet this criterion were considered protected.

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Acute Toxicity - Minimal Motor Impairment (MMI): To assess a compound's undesirable side effects (toxicity), animals were monitored for overt signs of impaired neurological or muscular function. In mice, the rotorod procedure is used to disclose minimal muscular or neurological impairment. When a mouse is placed on a rod that rotates at a speed of 6 rpm, the animal can maintain its equilibrium for long periods of time. The compound is considered toxic if the animal falls off this rotating rod three times during a 1-min period. In addition to MMI, animals may exhibit a circular or zigzag gait, abnormal body posture and spread of the legs, tremors, hyperactivity, lack of exploratory behavior, somnolence, stupor, catalepsy, loss of placing response and changes in muscle tone.

Compounds that were active in Test 1 (mice i.p.) were further screened in Test 2 (rat p.o.). Compounds retaining activity in Test 2 (rat p.o.) were selected for secondary evaluation (i.e., Test 3, Rat P.O. quantification) as explained below:

Secondary **Evaluation:** All quantitative *in vivo* anticonvulsant/toxicity evaluations of the active compounds were conducted at compound's time of peak pharmacodynamic activity (TPE). Groups of at least 8 rats received various doses of the candidate compound until at least two points were established between the limits of 100 percent protection or toxicity and zero percent protection or minimal toxicity. The 95 percent confidence limits, slopes of the regression lines and standard errors of the slopes were calculated for each quantitative determination. Rats received test compounds orally.

Test 1 screening results are presented in Table 1. Compound I-CA-MPD24 was active in both MES and scMET models and was shown to be non-toxic. However, some compounds were active in both MES and scMET models and were also shown to be

toxic. The compounds (i.e., I-A1-PD4, 1-AA-MPD12, 1-CA-MPD23, 1-A1-PD5, 1-Al-NOPD3, 1-CA-MPD24, 1-A1-PD15, I-CA-MPD25, and I-AA-MPD11) that are shown to be active in MES but showed no or mild toxicity were selected for Test 2 screening and those results are presented in Table 2.

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Three of the compounds (i.e., I-A1-PD4, 1-AA-MPD12, and I-A1-NOPD3) were considered for secondary evaluation, where quantification of their antiepileptic activity and neurotoxicity in rats (p.o.) was carried out. This secondary evaluation determines the time to peak effect (TPE), neurotoxicity, median effective dose (ED50) and biological response. The 95% confidence interval, the slope of the regression line, and the standard error are then calculated. The results of secondary evaluation (Test 3) are presented in Tables 3A and 3B.

Table 1: Primary Screening (Test 1) data for Anticonvulsant Activity and Neurotoxicity in Mice (test compound administered i.p.)

Compd	MES ^{a,b}		ScM	ScMET ^{a,c}		d
	,				Toxicity	a,d
	0.5 h	4.0 h	0.5 h	4.0 h	0.5 h	4.0 h
I-A1-PD7	+ (1/1)	-	+ (1/1) ^e	-	+ (2/4) ^d	_
I-A1-PD8	++ (2/3)	-	-	-	-	-
	+ (1/1)	+(1/1)	+ (1/1)	-	+ (4/4) ^f	-
I-A1-PD4	-	+++ (1/1)	-	_	_	-
	++ (1/7)	++ (3/3)	-	_	-	-
	+ (2/5)	+(1/1)	-	-	-	-
I-AA-	-	++ (3/3)	-	-	_	-
MPD12	nd	++ (1/3) ^g	nd	nd	nd	nd
	-	+(1/1)	-	-	-	-
I-CA-	-	++ (1/3) ^h	_	_	-	-
MPD23	-	+ (1/3)	-	-	-	-
I-A1-PD13	+ (1/1)	_	+ (1/1)	-	+ (1/4)	-
I-A1-PD5	+(1/1)	-	+ (3/5)	-	+ (3/4) ⁱ	-
I-A1-PD6	+ (1/1)	_	+(1/1)	_	+ (4/4) ⁱ	_
I-A1-PD10	_	-	_	_	++ (8/8) ^j	nd

I-AA-	-	-	+ (1/1)	-	+ (4/4) ^j	-
MPD13						
I-A1-NOPD1	++	-	_		-	-
	(1/3) ^k	_	+ (1/1)	-	+ (4/4) ⁱ	-
	+ (1/1)					
I-A1-NOPD3	_	++ (1/3)	+-		+++ (1/4)	-
	-	+ (1/1)	(1/1) ^l	-	_	~
			-			
I-CA-	-	++ (3/3)	-	_	-	-
MPD24	-	++ (3/3) ^h	-	-	_	-
	-	+	-	+	-	-
		(3/3) ^m		(1/1) ^l		
I-A1-PD15	+	++ (2/3)	-	-	-	-
	(1/1)	+ (1/1)	_	-	-	-
	-					
I-CA-	+	++ (2/3)	-	-	-	-
MPD25	(1/1)	+ (1/1)	-		-	-
	-					
I-AA-	_	++ (3/3)	-	-	-	-
MPD11	+ (1/1)	+ (1/1)	_	-	+ (1/4)	_

^aKey: +++ = activity or toxicity at 300 mg/kg, ++ = activity or toxicity at 100 mg/kg, +
= activity or toxicity at 300 mg/kg, - = no activity or no toxicity at 300 mg/kg.

^bMaximal electroshock seizure test. ^cSubcutaneous pentylenetetrazol seizure test.

^dNeurological toxicity (number of animals exhibiting toxicity/number of animals tested). ^e(number of animal protected/number of animal tested). nd = not determined.

^fLoss of righting reflux. ^gAt 6 hours after dosing. ^hAt 2 hours after dosing. ⁱUnable to grasp rotorod. ^jDeath. ^kAt 0.25 hours after dosing. ⁱMyoclonic jerks. ^mAt 6 hours after dosing.

10 Table 2: Screening (Test 2) data for Anticonvulsant Activity and Neurotoxicity in Rats (test compound administered p.o.)

Compd	Dose (mg/kg)	Time (h)	MES ^{a,b}	Toxicity ^{e,d}
I-A1-	30	0.50	0/4	0/4
PD4		1.00	1/4	0/4
		2.00	3/4	0/4
		4.00	4/4	0/4
I-AA-	30	0.50	0/4	0/4
MPD12		1.00	0/4	0/4
		2.00	1/4	0/4
		4.00	3/4	0/4
I-CA-	150	2.00	4/4	0/4
MPD23		4.00	4/4	0/4
		6.00	4/4	0/4
		8.00	4/4	0/4
I-A1-	50	0.50	0/4	0/4
PD5		1.00	0/4	0/4
		2.00	1/4	0/4
		4.00	1/4	0/4
I-A1-	30	0.50	· 0/4	0/4
NOPD3		1.00	2/4	0/4
		2.00	1/4	0/4
		4.00	4/4	0/4
I-CA-	30	0.50	0/4	0/4
MPD24		1.00	2/4	0/4
		2.00	3/4	0/4
		4.00	4/4	0/4
I-A1-	30	0.50	0/4	0/4
PD15		1.00	1/4	0/4
		2.00	3/4	0/4
		4.00	4/4	0/4
I-CA-	30	0.50	0/4	0/4
MPD25		1.00	3/4	0/4

		2.00	4/4	0/4
		4.00	2/4	0/4
I-AA-	30	0.50	0/4	0/4
MPD11		1.00	2/4	0/4
		2.00	1/4	0/4
		4.00	4/4	0/4

^aMaximal electroshock seizure test. ^b(number of animal protected/number of animal tested). ^eNeurological toxicity. ^d(number of animals exhibiting toxicity (i.e., atoxia)/number of animals tested).

5 Table 3A: Screening (Test 3) data for Anticonvulsant Activity (Time to Peak Effect) and Neurotoxicity in Rats (test compound administered p.o.)

Compd	Dose	Time	Time to Pea	ak Effect	Toxicity ^{d,e}
	(mg/kg)	(h)	MES ^{a,b}	ScMET ^{b,c}	(mg/kg)
				(50 mg/kg)	
I-A1-	10	4.0	4/4		
PD4		6.0	3/4	ļ	
		8.0	2/4		
		24	0/4		
	30	0.25	2/4	1/4 ^f	0/4 (100)
		0.5	2/4	0/4	0/4 (100)
		1.0	2/4	2/4	0/4 (100)
		2.0	2/4	1/4 ^g	0/4 (100)
		4.0	4/4	0/4	
I-AA-	15	6.0	2/4		
MPD12		8.0	1/4		

	30	0.5	0/4		
		1.0	0/4	1/4	0/4 (50)
		2.0	1/4	0/4	0/4 (50)
		4.0	3/4	0/4	0/4 (50)
		6.0	4/4	1/4	0/4 (50)
		8.0	4/4	2/4	0/4 (50)
		24	2/4	0/4	0/4 (50)
		8.0			1/8 (100) ^h
I-A1-	30	0.25			0/8 (500)
NOPD3		0.5			0/8 (500)
		1.0			0/8 (500)
		2.0	1/4	0/4	0/8 (500)
		4.0	3/4	0/4	0/8 (500)
		6.0	3/4	1/4	1/8 (500)
		8.0	4/4	3/4	0/8 (500)
		24	3/4	1/4	

^aMaximal electroshock seizure test. ^b(number of animal protected/number of animal tested). ^cSubcutaneous pentylenetetrazole seizure test. ^dNeurological toxicity. ^e(number of animals exhibiting toxicity (i.e., atoxia)/number of animals tested). ^fDeath following continuous seizure. ^sPopcorn effect and continuous seizure activity. ^hMild ataxia only.

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Table 3B: Screening (Test 3) data for Anticonvulsant Activity (ED50 and Biological Response and ED_50) in Rats (test compound administered p.o.)

Compd		EI) 50 Values a	nd Biologic	cal Response	
	Tim e (h)	Dose (mg/kg)	MES ^{a,b}	ED ₅₀	95% Confidence Interval Low/High	Slope/Std.Er

I-A1-	4	1.9	0/8			
PD4]	3.8	4/8			
		7.5	4/8	6.55	3.56/10.72	2.27/0.63
		15	7/8			
		30	7/8			
I-AA-	6	7.5	0/8			
MPD12		15	5/8	17.1	9.98/25.8	3.2/0.95
		30	7/8			
		60	7/8			
I-A1-	8	3.8	3/8			
NOPD3		7.5	3/8			
]	15	4/8	10.1	2.99/17/44	1.61/3.15
		30	9/12	:		
		60	8/8			

^aMaximal electroshock seizure test. . ^b(number of animal protected/number of animal tested).

I-A1-PD4 is a simple prodrug of lamotrigine. For this prodrug, ED50 for the MES model was determined to be 6.55 mg/kg and the time to peak effect was found to be 4.0 h after drug administration at doses of 10 as well as 30 mg/kg. This compound has shown moderate protection in scMET models where one out of four animals were protected at 0.25 h and 2.0 h period and two out of four animals were protected at 1.0 h after administration of the drug at a dose of 50 mg/kg. For the toxicity analysis, none of the animals given 100 mg/kg showed signs of toxicity.

I-AA-MPD12 is a mutual prodrug of lamotrigine and gabapentin ethyl ester. For this compound, ED₅₀ for the MES model was found to be 17 mg/kg and the time to peak effect was found to be 6.0-8.0 h at a dose of 30 mg/kg and indicated a significant extension protection (2 out of 4 animals were still protected) at 24 h after drug administration. Surprisingly, this compound, although less potent than lamotrigine, has exhibited significant extension in the duration of protection. At 50 mg/kg, none of the animals exhibited toxicity. However, at 100 mg/kg, one of eight animals exhibited mild ataxia.

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I-A1-NOPD3 is a NO-releasing prodrug of lamotrigine. For this prodrug, ED50 for the MES model was determined to be 10.1 mg/kg and the time to peak effect was found be at 8.0 h at a dose of 30 mg/kg and revealed a significant extension of protection (3 out 4 animals were still protected) even at 24 h after drug administration. Surprisingly, this prodrug, although less potent than its parent drug, has exhibited significant extension in the duration of protection. At 50 mg/kg, this compound has also exhibited significant protection (3 out of 4 animals were protected at 8 h after drug administration) in scMET rat model. For the toxicity analysis, only one in eight animals exhibited toxicity at 6.0 h time point at a dose of 500 mg/kg. At other time points (i.e., 0.25 h, 0.5 h, 1.0 h, 2.0 h, 4.0 h, 8.0 h after drug administration), none of the animals (0/8) exhibited any significant toxicity at the high dose of 500 mg/kg.

Biological Example 2:

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The pharmacological experiments on NO-releasing aspirin prodrugs were carried out by following the procedures described herein:

Animals and Procedures:

Male or female Sprague-Dawley rats weighing 150-200 g were used in the study. The rats were fed normal standard laboratory chow and maintained under standard conditions (room temperature of 22 ± 2 0 C; 50 ± 10 % relative humidity; artificial light 06:00 to 18:00). All experimental procedures mentioned below are approved by institutional animal research committees and were performed in accordance with standard guidelines for the treatment of animals.

Sample preparation and standard curve:

HPLC: Waters Allience analytical HPLC equipped with 2996 PDA detector and Empower software were used to analyze the samples.

25 HPLC Column: Waters X-Terra RP-18 analytical column, 150 X 3.9 mm, 5 μ.

HPLC Method: Flow: 1 mL/min, detecter set at 210 nm and at Maxplot (210-400 ran range). Solvent A: Acetonitrile; Solvent B: 0.1% TFA in water. Elution method: A linear gradient of 0-100% A.

Plasma samples were processed by transferring 75 µl quantity of blood into a test tube containing 250 µl acetonitrile, vortex-mixed and centrifuged at 1000 g for 5 min. 200 µl of supernatant was then taken and diluted to 2 times with acetonitrile. 100 µl of

the sample was injected into HPLC for analysis. Salicylate standard curves were generated using acetonitrile as solvent in the working range of 1-100 μg/ml.

Pharmacokinetic parameters were calculated using WinNonlin software (4.1 version). Cmax, Tmax, AUC 0-24, AUC 0-infmity, and Ty₂ characterized and each curve generated following oral treatment.

In Vitro Plasma stability:

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The rationale is that the prodrugs would be hydrolyzed in-vivo before, during or after absorption to release the corresponding free drugs. Therefore, we tested whether the test compounds (I-C1-NOPD6, 1-C1-NOPD4, 1-C1-NOPD5A) released parent drug in rat plasma at 37 ° C after 30 minutes incubation. The compounds were extracted back into acetonitrile with rigorous vortex. The results suggested that all prodrugs tested except I-C1-NOPD6 were found to be converting to the expected metabolite (salicylate) of the parent drug (aspirin) as revealed by HPLC analysis. Even aspirin was completely metabolized to salicylate after 30 minutes of incubation with rat plasma indicating that all the test compounds released aspirin, which in turn converted into salicylate.

Pharmacokinetic studies:

The oral pharmacokinetics of the test compounds, I-C1-NOPD6, 1-C1-NOPD4, I-C1-NOPD5A and I-C1-NOPD5B was done in rats and the release profiles of salicylate from these compounds were analyzed by HPLC and the results were presented in Figure 1 and Table 4. Overnight fasted rats were fed with 35 mg/kg equivalent doses of aspirin and test compounds. Blood was collected from orbital plexus of test animals at various time points up to 24 hrs. As shown in Figure 1, the test compounds I-C1-NOPD4 and I-C1-NOPD5B indicated unexpected drug release profiles wherein the salicylate is released in a sustained and controlled manner starting from 1 hour through 12 hours. For I-Cl-NOPD5B, the plasma salicylate concentration was maintained between 50 and 75 µg/ml during this extended period of over 11 hours. This kind of plasma concentrations of the drug can result in significant extension of duration of action. For I-C1-NOPD4 also, the plasma salicylate concentration was maintained between 35 and 50 µg/mL during an extended period of over 11 hours. Although aspirin absorption (Figure 1) was highest during 0.5 - 6.0 hrs (during which period much of the damage to the gastrointestinal tract

of the subject occurs due to high concentrations of the drug), plasma salicylate concentration for aspirin and I-C1-NOPD4 were comparable during the period from 8 through 24 hours. Such sustained release profile of active drug from the prodrug is expected to cause negligible or insignificant gastrointestinal damage as the plasma concentration of the drug never reaches to the toxic levels. Similar release profile was observed with I-C1-NOPD5A but for a shorter period of time. Unexpectedly, we have also observed as recorded in Table 4, nearly equal drug AUC values for aspirin and I-C1-NOPD5B (i.e., 923.63 ± 182.08 for aspirin vs 951.98 ± 11.58 for I-C1-NOPD5B) which indicates that the prodrug is as bioavailable as its parent drug, but prodrug does not cause gastric damage. Surprisingly, neither the prodrug nor the salicylate was found in the plasma of the animals fed with I-C1-NOPD6 (data not included in the graph) at any point of time tested, the reasons for which are not known.

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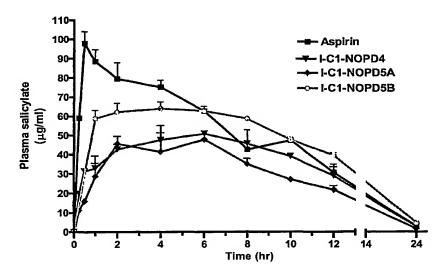


Figure 1. Plasma salicylate profile of aspirin and its NO-releasing prodrugs. The data values are expressed as Mean \pm S.E.M, n=3-4 animals. The data values at time points 6 and 10 hours is an average from two animals only.

Table 4. Comparison of pharmacokinetic parameters of aspirin and its nitro derivatives

Parameters*	Aspirin	I-C1-NOPD4	I-C1-NOPD5A	I-C1-NOPD5B
Cmax (µg/mL)	98.67 ± 12.64	53.24 ± 6.39	50.14 ± 10.12	66.08 ± 3.31
Tmax (h)	0.50 ± 0.00	4.66 ± 0.57	3.00 ± 0.57	4.00 ± 0.81

AUC _{0⁻24h} (h.μg/ml)	905.84 ± 173.14	749.36 ± 69.38	557.80 ± 97.65	922.89 ± 12.50
AUCo- _α (h. μg/ml)	923.63 ± 182.08	772.17 ± 75.68	565.30 ± 96.78	951.98 ± 11.58
Tin (h)	3.56 ±0.42	3.98 ± 0.25	3.35 ± 0.32	4.14 ±0.24

^{*}The data values are mean \pm SEM, n = 3-4

Ulcerogenic activity:

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Gastrointestinal ulceration is a serious side effect associated with NSAIDs. The clinical uses of potent NSAIDs are greatly limited by its gastrointestinal toxicity. We tested ulcerogenic potential of the test compounds, I-C1-NOPD6, I-C1-NOPD4, I-Cl-NOPD5A, and I-C1-NOPD5B in rats. Overnight fasted rats were given orally 100 mg/kg equivalent doses of aspirin and prodrugs (in the case of I-C1-NOPD5A and I-Cl-NOPD5B, 200 mg/kg equivalent doses were administered). The animals were sacrificed at 3 hours after drug administration. Stomachs of treated rats were separated, perfused with 10 ml of 2 % formalin, and then cut open over the greater curvature. The severity of the mucosal damage was then assessed on the basis of size (area) of the observed ulcers under surgical microscope with a square grid as per the established procedure (Takeuchi et al., J. Pharmacol. Exp. Ther. 1998, 286 (1), 115-121). Interestingly, none of the animals treated with the test compounds showed any signs of development of ulcers. However, severe haemorrhagic lesions (Mean ± S.E.M.: 2.7 ± 0.9 mm²) were seen in aspirin treated rats.

Anti-inflammatory activity:

Anti-inflammatory activity of test compounds was measured in carrageenan-induced rat paw edema model (Takeuchi et al., J. Pharmacol. Exp. Ther. 1998, 286 (1), 115-121). The activity of aspirin and test compounds (75 mg/kg equivalent dose of aspirin) is shown in Table 5. Aspirin at 75 mg/kg, p.o. exhibited anti-inflammatory activity from 1 hr through 6 hr with peak maximal activity at 4 hr. I-C1-NOPD4 showed significant activity during the first two hours after drug administration but its activity was not as good as that of aspirin from 2 hr through 6 hr. Surprisingly, I-C1-NOPD5A showed negligible anti-inflammatory activity at any time point tested (data not incorporated). We have not yet evaluated I-Cl-NOPD5Bin this efficacy test.

Table 5

Compound	Rat paw edema (% inhibition) Mean ± SEM, n = 6				
	1 hour	2 hour	4 hour	6 hour	
Aspirin	31.0 ± 7.2	52.5 ± 3.4	60.7 ± 6.9	42.8 ± 6.9	
I-C1-NOPD4	42.4 ± 13.3	44.9 ± 12.9	24.3 ± 7.7	8.6 ± 5.1	

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The results indicate the following:

- 1. Sustained release of the active drug over a period of 10-11 hours, which is good for twice daily dosage regimen, and
- 2. Exceptional gastrointestinal safety even at high equivalent doses of prodrugs compared to aspirin, which caused severe ulcers at equivalent doses.

We claim:

1. A compound of formula (I) or pharmaceutically acceptable salts thereof:

$$D^{1} \stackrel{L^{1}}{=} A \stackrel{A}{=} A^{1} \stackrel{L}{=} L^{2} \stackrel{D^{2}}{=} D^{2}$$
Formula (I)

wherein,

a is 0-2;

B independently represents a bond, $(CH_2)_b$, $(CH_2CH_2O)_c$, S-S, S-S=O, S-SO₂ or S-S=NH; b is 1-6; c is 1-1000;

A and A¹ independently represent a bond, (CH₂)d, 1,2-phenylene, 1,3-phenylene or 1,4-phenylene;

d is 1-8;

D¹ represents a therapeutic agent comprising one or more of the functional groups selected from the group consisting of -OH, -SH, -NHR¹, -CO₂H, -CONHR¹, -OCC=O)NHR¹, -SO₂NHR¹, -OSO₂NHR¹, -N(R^CC=O)NHR¹ and -N(R^SO₂NHR¹; D² independently represents D¹, a peptide, protein, monoclonal antibody, vitamin, R², R³, R⁴, NO, NO₂, NONOate or any other nitric oxide-releasing group or molecule, a group or molecule comprising one or more of water-solubilizing functional groups, a polymer or an amino acid;

E independently represents CH2 or a bond;

L¹ and L² independently represent a bond, O, S, NR¹, L, or a linkage selected from the group consisting of:

L is R¹² or a group with bonding in any direction, independently selected from the group consisting of:

X independently represents a bond, C, O, S, or NR¹;

Y independently represents a bond, C=O, C=S, S=O, SO₂, P(O)XR⁻¹, or (CH₂)_d; wherein d is as defined;

Z independently represents a bond, or (CH₂)J; wherein, j is 1-4;

 R^1 independently represents a bond, H, (d-CsJalkyl, substituted(Ci-Cs)alkyl, (C_5 - C_{14})aryl, aralkyl or M^{6+} ;

R² independently represents H, NH₂, or NHAc;

R³ independently represents H, CO₂R⁵ or CH₂CO₂R⁵;

R⁴ independently represents H, OH, O-(C]-C₈)alkyl, OM^{e+}, or a group selected from the group consisting of:

$$CO_{2}R^{6}$$

$$CH_{2}CO_{2}R^{6}$$

$$CH_{2}CO_{2}R^{6}$$

$$CO_{2}R^{6}$$

$$CO_{2}R^{6}$$

$$CO_{2}R^{6}$$

$$CO_{2}R^{6}$$

$$CO_{2}R^{6}$$

$$R^{10}$$

$$CO$$

M independently represents Na, K or a pharmaceutically acceptable metal ion; e = 1-3;

 R^5 independently represents at each occurrence H, M^{c+} , (Ci-Cs)alkyl, (C3-C8)cycloalkyl, substituted (C5-Ci4)aryl, hetero(C2-C14)aryl, C(=O)(CH2)fCHR9CO2R5, CH2C(=O)OR5, P(=O)(OR5)2,

$$CO_2R^6$$
, $CH_2CO_2R^6$, CO_2R^6 , CO_2R

X² independently represents O, S, SO, SO₂, or NR⁵;

 R^6 independently represents H, Na⁺, K⁺ any other pharmaceutically acceptable metal ion, (C_1-C_8) alkyl, or (C_3-C_8) cycloalkyl;

R⁷ independently represents at each occurrence same or different R⁵;

R⁸ independently represents CH₂, O, NR⁴, S, S=O or O=S=O;

R⁹ independently represents H, (Ci-C₈)alkyl or an amino acid;

f is 0-6;

g is 0-1;

h is 1-2000;

i is 1-4;

 R^{10} and R^{11} independently represent H, (Ci-C₈)alkyl, (C₃-C₈)cycloalkyl, or a group selected from the group consisting of:

with a proviso that when R^{10} is selected from the above group, R^{11} represents H or (C1-C₈)alkyl, and when R^{11} is selected from the above group, R^{10} represents H or (C₁-C₈)alkyl;

R¹² independently represents a group selected from the group consisting of:

 X^3 is independently 0 or NR⁷.

2. The compound according to claim 1, wherein a is 0.

- 3. The compound according to claim 2, wherein D² is a group or molecule comprising one or more water solubilizing functional groups selected from the group consisting of hydroxyl, amino, acylamino, carboxyl, sulphate, sulfonate, phosphate, phosphonate, N-acylsulfonamide, N-acylsulfamate, N-acylcarbamate, N-acylcarbamate metallic salts, and amino acids to form water-soluble prodrugs.
- 4. The compound according to claim 2, wherein D² is selected from the group of amino acids consisting of Alanine, Arginine, Asparagine, Aspartic acid, Cysteine, Glutamine, Glutamic acid, Glycine, Histidine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, and Valine.
- 5. The compound according to claim 2 wherein D^2 is a polymer.
- 6. The compound according to claim 5, wherein the polymer is selected from the group consisting of dextran, modified dextran, arabinogalactan, polyamino acids, and polyethylene glycol.
- 7. The compound according to claim 6, wherein the polymer is a polyaminoacid selected from group consisting of poly(l-glutamic acid), poly(d-glutamic acid), poly(dl-glutamic acid), poly(dl-aspartic acid), poly(dl-aspartic acid), poly(dl-aspartic acid), copolymers of the polyaminoacids and polyethylene glycol, polycaprolactone, polyglycolic acid, polylactic acid, polyacrylic acid, poly(2-hydroxyethyl 1-glutamine), dextran aldehyde, carboxymethyl dextran, arabinogalactane aldehyde, carboxymethyl arabinogalactane, and hyaluronic acid.
- 8. The compound according to Claim 5, wherein the polymer has a molecular weight of about 5000 to about 100,000 Daltons.
- 9. The compound according to Claim 5, wherein the polymer has a molecular weight of about 10,000 to about 50,000 Daltons.
- 10. The compound according to claim 2 wherein D^2 is a dipeptide.
- 11. The compound according to claim 2, wherein D² is a vitamin selected from the group consisting of vitamin A, vitamin C, thiamine, folic acid, biotin, inositol, nicotinic acid, nicotinamide, riboflavin, pyridoxine, pyridoxal 5-phosphate, ergosterol, vitamin D2, vitamin D3, vitamin D4, vitamin E, menadoxime, menadiol, and vitamin K5.

12. The compound according to claim 2, L^2 is O; A and A¹ are independently $(CH_2)_d$, 1,2-phenylene, 1,3-phenylene, or 1,4-phenylene; d is 1-4; B is S-S, S-S=O, S-SO₂ or S-S=NH; D^2 is NO, NO₂ or a NONOate selected from the group consisting of:

13. The compound according to claim 2, wherein L² is O; A and A¹ are CH₂; E is CH₂; B is a bond or (CH₂)b; b is 1-6; a is O; D² is NO₂ and L¹ is a group selected from

wherein,

X is O, S or NR1; and

Y and Z are as defined.

14. The compound according to claim 2, selected from the group consisting of:

WO 2006/027711 PCT/IB2005/052797 213

$$H_3C$$
 H_3C
 H_3C

I-Taxol-PD2

- 15. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 2, or a pharmaceutical salt thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.
- 16. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 14, or a pharmaceutical salt thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.
- 17. The compound as in claim 2, wherein D¹ and D² represent known and investigational amino-, hydroxyl-, carboxyl-, and keto- containing drugs compiled in drug databases comprising the Merck Index, IDdb, Prous Science's Integrity[®], Prous Science Drugs of the FutureTM, and The Ensemble[®].
- 18. The composition of claim 15 comprising therapeutically effective amount of pairs of drugs selected from: Paclitaxel and Doxorubicin; Paclitaxel and Mitomycin C; Paclitaxel and 9-aminocamptothecin; 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP), 3-Ammopyridine-4-methyl-2-carboxaldehyde thiosemicarbazone (3-AMP) and Paclitaxel, Doxorubicin, Mitomycin C; CC-1065 and Paclitaxel, Doxorubicin, Mitomycin C; Trans-Resveratrol [(E)-3,4',5-trihydroxystilbene)

and Paclitaxel, Doxorubicin, Mitomycin C; Retinoic acid and Butyric acid; Paclitaxel and Captopril; Doxorubicin and Biotin; 5-Fluorouracil and Cytarabine; Edatrexate and Paclitaxel; Cephalosporanic acid and Paclitaxel; Cephalosporin and Paclitaxel; Paclitaxel and Gemcitabine; Levodopa and Carbidopa; Amoxicillin and Clavulanic acid; Ampicillin and Clavulanic acid; Amoxicillin and Pencillinic acid sulfone; Ampicillin and Pencillinic acid sulfone; Olivanic acid and 3-substituted Z-2-acylaminopropionic acid; Lifibrol and Lovastatin/Pravastatin/Fluvastatin/Atorvastatin/Simvastatin; Ezetimibe and Lovastatin/ Fluvastatin/Atorvastatin/Simvastatin; **Amlodipine** and Pravastatin/ Lovastatin/Pravastatin/Fluvastatin/Atorvastatin/Simvastatin; Metformin and Nateglinide/Glipizide/Glibenclamide (Glyburide): Metformin and Lovastatin/Pravastatin/Fluvastatin/Atorvastatin/Simvastatin; Pseudoephedrine and Fexofenadine/Cetirizine/Desloratadine/Epinastine; Salbutamol and Ipratropium bromide; Mometasone and Formoterol/Salmeterol; Fluticasone and Formoterol/Salmeterol; Budesonide and Formoterol/Salmeterol; Declofenac and Misoprostol; Declofenac and Omeprazole/Lansoprazol/Rabeprazole/Leminoprazole/Pantoprazole; Naproxen Prophenazone; Acetaminophen and chlorzoxazone/metaxalone/mephenoxalone; Zidovudine and Lamivudine; Triple prodrug of Zidovudine; Lamivudine and Abacavir (Ziagen); Lopinavir and Ritonavir; Lamivudine and Adefovir/dipivoxil; Amprenavir and Zidovudine; Nelfinavir and Zidovudine/Lamivudine; Stavudine and Zidovudine/Lamivudine; Dideoxyinosine and Zidovudine/Lamivudine; Emtricitabine and Penciclovir/Famciclovir; Acyclovir and deoxycholate/chenodeoxycholate ursodeoxycholate; Triple and Zidovudine; and Lamivudine and Efavirenz;

- 19. A therapeutically effective amount of the pharmaceutical composition as in claim 15, comprising a two or more drugs, a drug and its own prodrug, a drug and a different prodrug, two different prodrugs, a drug and a mutual prodrug, mutual prodrug and its own drugs or a mutual prodrug and one of its constituent drugs.
- 20. The compound according to claim 2, wherein D¹ and D² are therapeutic agents selected from the group consisting of: Sedatives, Hypnotics, Antidepressants, Antipsychotics and Antimanics, Analgesics, Antipyretics, Antimigraine agents, Anticonvulsants, Drugs used in parkinsonism and movement disorders, Drug for dementia, Antiemtics, drugs for Vertigo, CNS Stimulants activators; Antiinfective eye

Antiinflammatory; antiallergic preparations, antiglucoma preparations; preparations to cure eye diseases; aural, nasal and oropharyngeal preparation, Antiarrhythemic drugs, Antihypertensives, alfa/beta-blockers, channel blockers, ACE inhibitors, Angiotensin II receptor antagonists, diuretics, Antianginals, nitrates, calcium channel blockers, Drugs for cardiac failure and shock, Vasodilators, Coagulants, Anticoagulants, Thrombolytics, antiplatelet drugs, Respiratory stimulants, Antitissives, Expectorants, Mucolytics, Decongestants, Antihistamine agents, antiasthmatics; Antiulcer, Antisecretory drugs, H2 receptor antagonists, Proton Pump Iinhibitors, Prostaglandin analogues, Antacids, Antispasmodics, drugs modifying intestinal motility, Antidiarrhoeals, antimotility drugs, antimicrobial drugs, drugs acting on gall bladder, Urinary antiinfectives, Diuretics, Urinary analgesics, Antispasmodics, Antiinfective drugs acting on urethra and vagina, drugs acting on uterus, Drugs for prostatic hypertrophy, alfa blockers, antiandrogens, Drugs for erectile dysfunction, Spermicidals, nonhormonal contraceptives, Emollients, keratolytics, topical antiinfectives, topical antifungals, topical parasiticidals, topical steroids, topical drugs for acne vulgaris, drugs for psoriasis, pigmentation disorders, and Antiseborrhoeics, Non Steroidal Anti. Inflammatory Drugs (NSAIDs), COX-2 inhibitors, Antiarthritic agents, Immunosuppressants, Topical analgesics, Muscle relaxants, Neuromuscular Drugs, Penicillin antibiotics, Cephalosporin antibiotics, Quinolone, Fluoroquinolone antibiotics, antibiotics, Chloramphenicol, Tetracyline antibiotics, Antianaerobics, Metronidazole, Antitubercular drugs, Antileprosy drugs, Antifungals, Anthelminthics, Antiinfestive Drugs, Antimalarials, Anabolics, androgenic steroids, Corticosteroids, Oestrogens, Progestogens and Hormonal contraceptives, Fertility Agents, Trophic hormones and related drugs, Thyroid and antithyroid drugs, Antidiabetics and hyperglycaemics, Vitamins, Amino acids, Antiobesity drugs, Hypolipidaemic drugs, fibric acid derivatives, statins, HMG CoA reductase inhibitors, nicotinic acid group, drugs used for Gout, drugs affecting bone metabolism, bisphosphonates, Anticancer drugs, alkylating agents, cytotoxic antibiotics, antimetabolites, cytarbine, Fludarbine, 5-Fluorouracil, Mercaptopurine, Thioguanine, Vinca alkaloids, Etoposide, Taxanes, Topoisomerase 1 inhibitors, Cytotoxic immunosuppressants, Immunostmulants, Cytoprotectives, Amifostine, Oestrogens,

Progestogens, hormon antagonists, antineoplastic drugs, Antiallurgics, non-sedative antihistamins, Cetirizine, Desloratadine, Terfenadine, Fexofenadine, sedative histamines, histamine receptor blockers, Local anaesthetics, intravenous anaesthetics, inhalation anaesthetics, and muscle relaxants.

- 21. The compound according to claim 2, wherein D^1 and D^2 are from same or different therapeutic class and exhibit either the same or different mechanisms of action or work on same or different biological targets or work on same or different disease conditions.
- 22. A method of treating a mammal or human in need thereof comprising administering a therapeutically effective amount of the composition according to claim 15.
- 23. A method of treating a mammal or human in need thereof comprising administering a therapeutically effective amount of the composition according to claim 16.
- 24. A method of use of the compound according to claim 2, for prevention or treatment of diseases where a chronic, sustained and selective release of the constituent drug or nitric oxide is beneficial.
- 25. A method of use of the compound according to claim 2, in a subject in need there of for prevention or treatment of diseases of Central Nervous System, Eye, Ear, Nose and Oropharynx, Cardiovascular System, Respiratory System, Gastrointestinal tract system, Genito-urinary system, skin, musculo-skeletal system, Endocrine system, metabolism and neoplastic disorders, infectious diseases, allergy and immunology, and for anaesthetic, analgesic and surgical needs.
- 26. A method of treating a mammal or human in need thereof comprising administering a therapeutically effective amount of two or more compositions according to claim 15, wherein compositions used in combination to treat a patient in need of a combination therapy.
- 27. A method of use of composition as claimed in claim 15, for prevention and/or treatment of diseases where a chronic, sustained and selective release of the constituent drug(s) and/or nitric oxide is beneficial.

28. The novel intermediates obtained in the preparation of compounds of claim 1, wherein the intermediates are selected from:

$$\mathsf{HO} \overset{S}{\longrightarrow} \mathsf{S} \overset{O}{\longrightarrow} \overset{\mathsf{CH}_3}{\longrightarrow}$$

2-((2-Hydroxyethyl)disulfanyl)ethyl acetate (LI-1a)

2-((2-(Trityloxy)ethyl)disulfanyl)ethanol (LI-1c)

2-((2-Hydroxyethyl)disulfanyl)ethyl nitrate (LI-2b)

2-((2-Hydroxyethyl)disulfanyl)ethyl nitrate (LI-2c.TFA)

tert-Butyl 2-((2-bromoethyl)-disulfanyl)ethylcarbamate (LI-2e)

1,2-Bis(2-bromoethyl)disulfane (LI-3a)

2-((2-Aminoethyl)disulfanyl)ethyl nitrate.acid salt (LI-5.TFA)

2-((2-(Tetrahydro-2*H*-pyran-2-yloxy)ethyl)disulfanyl)ethanol (**LI-1b**)

2-((2-Hydroxyethyl)disulfanyl)ethyl 2-chloroacetate (**LI-1d**)

$$B_r$$

2-((2-Bromoethyl)disulfanyl)ethanol (LI-2a)

$$HO$$
 $S \sim S$ $M \sim Boc$

tert-Butyl 2-((2-hydroxyethyl)disulfanyl)ethylcarbamate (LI-2c)

$$H_{3C}$$
 S O S S M Boc

2-((2-(tert-Butoxycarbonylamino)ethyl)-disulfanyl)ethyl methanesulfonate (LI-2d)

$$O_2N_O$$
 S_S M_{Box}

tert-Butyl 2-((2-(nitrooxy)ethyl)-disulfanyl)ethylcarbamate (LI-2f)

$$O_2N_O$$
S $_S$ O $_{NO_2}$

2,2'-Disulfanediylbis(ethane-2,1-diyl) dinitrate (LI-3b)

$$H_2N$$
 S_S O_NO_2

2-((2-Aminoethyl)disulfanyl)ethyl nitrate (LI-5)

2-((2-Bromoethyl)disulfanyl)ethyl carbonochloridate (LI-6)

- 29. The use of the novel intermediates of claim 26, in the preparation of compounds of formula I or pharmaceutically acceptable salts thereof.
- 30. The process for the preparation of the compound as in claim 1, or a pharmaceutically acceptable salts thereof, wherein the process is selected from:

Process 1: A) Monoprotection of Bis-(2-hydroxyethyl)disulphide (SL-I) with an appropriate hydroxyl protecting group to give the corresponding monoprotected intermediate LI-Ix,

disulfanyl)ethyl 2-(dimethylamino)ethylcarbamate (LI-10)

B) Converting LI-Ix, obtained in step A to an activated formyl intermediate LI-lxy by treating with phosgene or its equivalent, and

- C) Reacting LI-lxy obtained in the step B with an appropriate amino- or hydroxyl containing drug (D¹) to give the corresponding compound of formula I;
- Process 2: A) Converting carboxyl containing drug (D l) into its activated acyl halide or imidazolide or isocyanate by known methods, and
- B) Reacting the intermediate obtained in the step A with the linker intermediate LI-Ix to obtain the compound of formula I;
- Process 3: Mixing a selectively protected and activated drug with a solution of 2-((2-hydroxyethyl)dithio)ethyl nitrate (LI-2b) in a suitable solvent in presence of a suitable coupling agent to obtain the compound of formula I and pharmaceutically acceptable salt thereof, wherein D² is NO₂;
- Process 4: Converting 2-((2-hydroxyethyl)dithio)ethyl nitrate (LI-2b) into its formyl halide or imidazolide (LI-4x) by using a phosgene or its equivalent reagent and mixing/reacting the resulting reactive intermediate with a suitable amino- or hydroxycontaining drug in suitable solvent in presence of a suitable base to obtain the compound of formula I and pharmaceutically acceptable salt thereof, wherein D² is NO₂;
- Process 5: Mixing/reacting a an appropriately protected and activated drug with a solution of 2-((2-aminoethyl)dithio)ethyl nitrate (LI-5) in a suitable solvent in presence of a suitable coupling agent and/or base to obtain the compound of formula I and pharmaceutically acceptable salt thereof, wherein D² is NO₂; and
- Process 6: A) Monoprotection of Bis-(2-hydroxyethyl)disulphide (SL-I) with an appropriate hydroxyl protecting group to give the corresponding monoprotected intermediate LI-Ix,
- B) Reacting formyl linker intermediate LI-lxy with amino or hydroxyl containing drug
- (D) to obtain the prodrug of formula I with free hydroxyl group on the linker,
- C) Converting the intermediate obtained in the step B into activated formyl halide or imidazolide derivative, and
- D) Reacting the intermediate obtained in the step C with the drug D^2 to obtain the mutual prodrug of formula I.

From the INTERNATIONAL SEARCHING AUTHORITY	PCI	
To:		
VEPACHE) DU PROFESSIONAL CORPORATION		
Atta. vepach.edu, sreenivasara	NOTIFICATION OF DECISION CONCERNING	
3.230 Georgetown Way	PEOLIFICATION	
Vernon H.Ule, IL 60061	REQUEST FOR RECTIFICATION	
UNITED STATES OF AMERICA		
	(PCT Rule 91,1 (f))	
	Date of mailing	
	(day/manthfyean 16/02/2006	
Applicant's or agent's file reference	RI=PLY DUE	
NP-2005-001	NONE However, see last paragraph below	
International application N",	International filing data	
	(dβy/moπth/yaar) 26/08/2005	
PCT/ S 2 0 0 5 / 052797	20/08/2003	
Applicant		
SATYAM, Appara α		
The applicant is hereby notified that this International Searching Authority has considered the request for rectification of obvious errors in the International application/in other papers submitted by the applicant to this Authority, and that it has decided:		
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 to authorise the rectification; 		
as requestor] by the applicant,		
to the extant set forth below*;		
 J£ to refuse to authorize the rectification or part of it for 	the following reasons*:	
Request received too late by ISA/EP. See RuIa 91.Kg) (i) PCT.		
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A copy of this notification, together with a copy of the applicant's request for rectification, has been sent to the receiving Office and to the International Bureau.		
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	ļ	
* If the authorization of the rectification has been refused in Whole or in part, the applicant may request the International		
Bureau, before the technical preparations for international publication have boon completed and subject to the payment of a fee, b publish tha request for rectification together with the international application. See Rule 91.1(f), third and fourth		
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NL-22BD HV RIJswijk	Sylvia Hermier	
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1 47. (-01 10) 0 00 10		

IN THE EUROPEAN PATENT OFFICE

5	Applicant: Apparao Satyarø et at International Application No.; PCT/IB2005/052797 International Filing Date: August 26, 2005) Atty. Docket No.: NP-2005-001) RE: Rule 9 1 Rectification) Date: January 2S₁ 2006)
10	Titlet PRODRUGS CONTAINING NOVEL BIO-CLEAVABLE LINKERS)))
15	Ifltejtftational Searching Authority Patentlaan 2 22S8EERijswijk The Netherlands Fax: 0031703403016	

20 REQUEST EPR RECTIFICATION UNPERRULE 91

Dear Sir;

In the above referenced patent application, applicants submit the following supplementary tentification under jrøle 91 for entry prior o publication.

25 1) Rectifications to PCT-SAEE Electronic Filling Errors.

Rectifications to the Specification begin on page 1 of this paper.

Rectifications to the Ctaims begin on page 4 of this paper.

2) Rectifieat ïofls to TypograpftJcal and Obvious Errors

Rectifications to the Specification begin on page 5 of this paper,

Rectifications to the Clahns begin on page 14 of this paper.

Remarks begin on page IS of this papejr.

Sabstitot- i Specificfltton and! Claims follow page 20 of this paper, with page numbers starting from 1,

1) Rectifications to PCT-SAFE Electronic Filing Errore:

During PCT-SAFE filing, blank spaces were introduced between schemes and between schemes and the text. The following rectifications to delete the inadvertently introduced spaces are respectfully requested,

5

I ωthe Specification:

Please delete the blank spaces on the following pages and rearrange the matter:

Pages 643

10 Ortpage 6, please delete blank space from line 24 to the end of the page.

Oa page 7, please delete blank spaces at the beginning and at the end of the page.

On page 8^please delete blank space at the end of the page.

Ofl page P, please delete blank space at the beginning of the page.

On page 10, please delete blank space at rtie end of the page.

On page 12, please delete blank space at the beginning of the page.

Oa page 13, please delete blank space at ffoe beginning of the page.

The corresponding pages in the {substitute specification provided herewith are pages 6-10.

Pages 23-30

20 On page 23, please delete blank space fron* line 25 to the end of the page.

On page 24, please delete blank space at the beginning of the page.

On page 25, please delete blank space at the end of the page.

On page 26, please delete blank space at the beginning of the page.

On page 27, please delete blank space f 0m line 12 to the end of the page

25 Ot* page 29, please delete blank space at the beginning of the page.

Oft page 30, please delete blank Space at the beginning of the page.

The corresponding pages in the substitute specification provided herewith ate pages 21-24.

Page 33

30 On page 33, please delete blank space between line 11 and the stnicttires.

The cotresponding page in the substitute specification provided herewilh is page 27-

Page 36

Oa page 36, please delete blank space between line 6 and the structures.

The corresponding pages in Uie substitute specification provided herewth are pages 29-30.

5

Pages 37-46

On page 37, please delete blank space from line 12 to the end of the page.

Oa page 38, please delete blank space at the end of the page.

On page 40_s please delete blank space at the end of the page,

10 On page 411, please delete Wank spaces at the beginning and at the end of the page.

On page 42₂ please delete Wank spaces at the beginning and at the end of the page.

On page 43> please delete Hank space at the end of the page,

On page 44, please delete blank space at the begintung of the page,

On page 46, please delete blank space after first two lines b flje end of the page.

15 The corresponding pages in the substitute specification provided herewith aw pages 31-37.

Pages 50-51

On page 50, please delete blank spaces at the beginning and at the end of the page.

Otx page 51, please delete blank space at the end of the page.

The co-responding pages in the substitute specification provided herewith ate pages 40-4 1.

Page 56

On page 56, please move the sentence at the e&d of the page to top of next page.

The corresponding page in the substitute specification provided herewith is page 45.

25

JPage59

On page 59, please move the sentence at \dot{u}_{R} end of the page to the top of next page.

The corresponding page in the substitute specification provided herewith is page 49-

30 Page 71

On page 713 please move the single on the page to the top of next page.

Tlic corresponding page in the substitute specification provided herewith is page 60.

Page 89-91

On page 89, please delete blank space at the end of page.

5 On page 90, please delete blank spaces at the beginning and at the end of úce page.

On page 91, please delete biack spaces at the end of the page.

The corresponding pages in the substitute specification provided herewith are pages 77-79.

Page 94

10 On page 94, please delete blank space at the end of the page.

The corresponding page in the substitute specification provided herewith is page 81.

Page 97-98

On page 97, please delete blank space between the structures.

15 On, page 9K please delete blank space at the beginning of the p≥

The coπώspondiüg pages in the substitute specification provided herewith are pages 84-85,

Page 103

On page 103, please delete blank space from line 6 to the end of the page.

20 The corresponding page in His substitute specification provided h β β wMi is page 90.

Pages 132 -133

On page 132, please delete blank space at the beginning of the page.

On page 133, please delete blank spaces at the beginning and at the end of the page.

25 The conespoi&ding page in the substitute specification provided herewith is 118.

Jn the Claims:

rages 203-231

On page 203, please delete Wank space at the end of the page.

30 Oa page 204, please delete blank space at the beginning of the page.

On page 205, please delete blank spaces at the beginning and at fb.e end of the page.

- On page 2G6, please $\dot{\alpha}eMe$ blank space at the beginning of the page.
- Oftpage 207, please delete blank space at the end of the page.
- On page 209, please delete blank space at the beginning of the page.
- On page 2103 please delete blank space at the beginning of the page.
- 5 On page 216, please delete blank space at the end of the page.
 - On page 2 17, please delete blank spaces at the beginning and at the end of (he page.
 - On page 222, please delete blank space at the end of the page.
 - On page 223, please delete bïauk space at the end of the page.
 - The corresponding pages in the substitute claims provided herewith are pages 188-210.

10

20TVFOGItAPH LAWDOTHER OBVIOUS ERRORS

RECTIFICATIONS TO THE SPECIFICATION

- 15 OD page (13
 - At Hue 7: Please insert V after "one".
 - The corresponding page in the substitute specification provided herewi Λ is page 10, line 7.
- 0 » page 15
- 20 At line 6: Please delete "and" after "secondary" and insert "and phenolic after "tertiary",
 - At line 8: Please delete "or" after "secondary" and insert "or phenolic" after "tertiajy".
 - At line 14; Please delete "cyclobutyl".
 - At line 17: Please insert "cyctøbutyP after "cyclopropyl".
 - At line 33: Please replace y with "." after "like".
- The corresponding pages in the substitute specification provided herewith, are page M_7 lines 7, 9, IS_7 and 1S and page 13, line 2,
 - On page 18
 - At line 6: Please insert "by" after "described".
- 30 The corresponding page in the substitute specification provided herewith is page 15, line 9.

At line 2: Please replace "then" with "the".

At Irae 22: Please introduce a space after "entirety."

5 At line 29: Replace "likes" with "like".

At line 31: Replace "likes" with "like".

The cowespojiding page in the substitute specification provided herewifti is page 19, line $3_{?}$ 23 and 30, and page 20, liae 2.

10 On page 33

At line 2: please replace "CH2CH" with "CH2CH2".

The cont-csponding page in the substitute specification provided herewith is page 27, line 2,

On page 35

15 At line 1: Please replace "erabodienint" with "embodiment" and "D2" with "D2".

The corresponding page in the substitute specification provided herewith is page - HAO-,

At line 9: Please replace "a" with "an".

The corresponding page in the substitute specification provided herewith is page 28, line 22.

20 O»p /gc36

At line z; Please replace "Rl" with "R 1".

The corø&ponding page in the substitute specification provided herewith is page 2% line 20.

On page 37

25 At line 8, please replace "Rl" with "R l".

The cacrespondiig page in the substitute specification provided herewith is page 30₃ line 21.

On page 38

Please jrøplace the incorrect structure of ICI-PDIO with the correct structure as shown below;

I-CI-PDIO

Ifoe corresponding page in the substitute specification provided herewith, is page 31.

On page 40

Please introduce (he missing I-AÏ-PD18 along with its structure as shown belowj

I-A1-PD18

10 The corresponding page in the substitute specification provided herewith is page 33,

Ott page 44

Please replace the incorrect structure of \ddot{l} -HWD14 with the correct structure as shown below;

15

I-H1-PDX4

The corresponding page in the substitute specification provided herewith is page 35.

20

Onpge49

Hease replace the incorrect structure of I-A1-NOKD6 with the correct structure as shown below;

I-A1-NOPD6

The corresponding page in the substitute specification provided herewith is page 39,

On page 51

Please introduce the missing \(\bar{l}\)-H1-N0FD11 along with its structure as shown below:

10

5

I-HI-NOPD11

The corresponding page in the substitute specification provided herewith is page 40.

15 Atline 14 below the srøictures please replace "Ptudrugfl" with "Prodrugs^

The cottespondiøg page in 1he substitute specification provided herewiώ is page 41>Hue 1.

Oh page W

Please replace the incorrect structure of I-CA-MPD22 with the correct structure as shown

20 belbw:

I-CA-MPD22

The corresponding page in &e substitute specification provided herewith is page 50.

5 On page 73

At line 5: Please replace ";" after the word "foimula F vrith ".".

The corresponding page in the substitute specification provided herewith is page 61, line 3.

On page 79

10 At line 16, please insert "comprises" after "invention".

The corresponding page in the substitute specification provided herewith is page 67, line 16.

On page 86

At Jincs 16-18, please change the text to bold font, add a space between line !5 and 16 and

delete the space between lines 17 and 18,

The corresponding page in the substitute specification piwided herewith is page 74.

On page 98

At line 6: Please replace "form" with "from"

20 At line 11: Please replace "Schotoea" with "Scheme".

The corresponding page in the substitute specification provided herewith is page 85, lines 2 and 7.

Out page 99

25 At line 1: Please insert "that" after "possible".

The wrresponding page in the substitute specification provided herewith is page 85, line 17.

On page 100

In Scheme M2 please replace "Inteπadediate" with "Interjtnediiate" before "Conjugate 'a".

30 The corresponding page in tile substitute specification provided herewith is page 89.

9 of 20

40 /00 100 TYDT 40 E.

At line 2: Please tepkce "generate" with "generate".

The corresponding page in the substitute specification provided herewith is page 92, line 2.

5

On page 1B6:

At line 2: Please delete "NO- releasing" and insert "of formula I" after "prodrugs".

Atline U: Please insert 'W *after "such".

At line 24: Please replace V -with "." after "lUmexoloiie"

10 At line 28: Please replace "," with "." afor "TixocortoF,

The corresponding page in the substitute specification provided herewith is page 92, lines 5, 14, 27atttd 31.

Oft page 112

15 At line 1: Please replace "keto-contia βmg" -with "keto-containiag*.

At line 111Please replace "\" with \" *after "propionic acid".

The corresponding page in the substitute specification provided herewith is page 98, line 1 and 12.

20 On page I W

At line 25: Please replace "transretinioc" with "trans-retino ic^

The corresponding page in Hie substitute specification provided herewith is page 99, line 25.

On page 117

25 At line 25: Please replace "includinig'* with "including".

The corresponding page in the substitute specification provided herewith is page 103, line 25.

O)D page 118

At Line 30: Please replace "Itranunostaiiilants" with "uranunostimulants".

30 The corresponding page in the substitute specification provided herewith is page 104, line 30.

At line 9' Please delete "NO-releasing"

At line 11: please replace "occasionally 1with "occasionally"

At line 24: Please replace "," with V after "Gemciiabine".

5 The corresponding page in the substitute specification provided herewith is page 105, lines 9, 11, and 24.

Oft page 120

At line 17: Please replace '?' with "." after the word "like".

10 At line 21: Please replace "PEPAT ITIS BMwi<3i 'HEPATI HS B".

At line 30, please delete "and" after "Triple",

The corresponding page in the substitute specification provided herewith is page 10(5, lines 17,21 and 30.

15 OB page 121

At line 1; Please delete the repeated word "ihe" before "pjesentf'_

At line 6: Please replace "shoud" with "should".

At line 7: Please delete "nitrate ester (NO-releasing)" after "form of.

At line 10: Please replace "composition." with "composition" after pharmaceutical and delete

20 "NO->5 alter "their".

At line 11: Please delete "releasing" before "prodrug".

At Uae 28; Please replace "ptacctatnol" with "paracetamol".

The corresponding page in the substitute specification provided herewith is page 107, lines 1, 6,7, 10, 11 3^28.

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Oβ page 150

At line 9, please replace "RTe" with "RT".

At line 13, please insert "was added" after "(5 mLf.

The corresponding page in the substitute specification provided herewith is page 135, lines 9 artdU.

At line 19, please replace "SchejmE 14, Method B" -tvith "Scheme 2".

The coiresponding page in the substitute specification provided herewith is page 136, line 19,

5 On page 152

At line 2, please replace 'Intermediate ' with "prodrug".

At line 24, please replace "SyntMs" wi& "Synthesis".

The corresponding page in the substitute specification provided herewith is page 137, lines 2 and 24,

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On page 154

At lino 18; Please insert hI-AMPD10" after "of.

The corresponding page in the substitute specification provided herewith is page 139, line 18,

15 Onpag&156

At line H >please delete "end" after "solution of*,

At line 28: Please replace "I-AI-PD16" with "Ï-A1-PD1S".

The corresponding page in the substitute specification provided herewith is page 141, line U and 28.

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On page 157

At line 8: Please replace "I-A1-PD16" with a "I-A1-PD1 δ ".

The corresponding page in the substitute specification provided herewith is page 142, line 8.

25 On page 158

At line 2, please insert "in" after "dissolved" before "DCM".

The corresponding page in the substitute specification provided herewith is page 143, line 2,

On page 160

30 At line 6, please insert "the above intermediate (2.5 mL) and" after "A mixture of.

The corresponding page in the substitute specification provided herewith is page 145, line 6,

At line 1, please insert "to the" after "according".

The corresponding page in the substitute specification provided herewith is page154> line 1.

5 On page 173

At line 22, please insert "BOC deprotected" after "solution of

At line 22, please insert and "and then deprotected using a known general deprotectfon method" after "Method C^M.

The corresponding page in the substitute specification provided herewith is page 158, lines 22 and 23,

On page 176

At line 25, please replace "15" with "17".

The corresponding page in Ihe substitute specification provided herewith is page 161, line 2S.

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On page 177

At line 2, please insert ":" at the end, and on line 2, please replace "15Hwith "t7".

The corresponding page in the substitute specification provided herewith is page 162, line 2,

20 On page 186 '

At lines 2-4, please delete the incorrect NMR data shown below;

¹H-MMR: (CDCl₃, 300 MHz): 2.21 (s_t 3H)> 2.36 (s, 3H), 2.93-3.05 (m, 2H), 3.19-3.28 (m, 2H), 3,88 (s, 3H), 3.92 (3, 3H), 4.70-4.87 fat, 6H), 7.10-7.50 (m, 3H), 8.10 (s, 1H).

The corresponding page in the substitute specification provided herewith is page 171» line 2.

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On page ISS

At line 8, please replace "122" with "114",

The corresponding page in the substitute specification provided herewith is page J73, lime 8.

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RECTIFICATIONS JQ THE CLATMS

Oa page 203

At time 2, please introduce ", novel metermediates in preparation thereof, after " $ft\pi\pi$ ula I", The corresponding page in the substitute claims provided herewith is page 188, line 2.

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On page 207

At line 2, please insert "or" after "K+".

The corresponding page in the substitute claims provided herewith is page 190, line 11.

10 On page 215

U the claim 14: Please replace &e incorrect snucture of **I-H1-P&14** with the correct structure as shown below:

I-H1-PD14

The corresponding page in the substitute claims provided herewith is page 197.

On page 216

In the clafo. 14> please replace the incorrect structure of **I-At-NOPD6** with title correct structure as shown below;

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The corresponding page in the substitute claims provided herewith is page 198,

In the claim 14, please introduce the inadvertenfly omitted structure of **I-HI-NOFDlt** with the correct structure as shown below:

5 The corresponding page in the substitute claims provided herewith is page 198,

On page 225

At line I4>please replace "Decjofenac" with "Diclofenac" at each occwaftca.

At line 22, please replace ";" with V after "Efavirenz".

The codxespondMig page in the substitute claims provided herewith is page 204» line 3.0 and page 205, line 7,

On page 230

At line 3 (in claim 29), please jeplace "claim 26" with "claim 28."

15 The corresponding page in the substitute claims provided herewith is page 209, line 3.

0 » page 231

At line 16, in process 5, please delete "a" before "an".

The corresponding page in the substitute claims provided herewith is page 210, line 16.

REMARKS

This communication addresses formatting ewors during PCT-SAFE Electronic filing of the above referenced application and, tinder rule 91, rectification of inadvertent typographical errors, fottnatttøg errors and omissions in the specification and claims as filed.

Upon recommendation of EP International Searching Authority (EP-ISA) in a telephone communication dated January 1\$, 2006, this communication includes and supersedes the earlier rectification request under 91 filed September 23, 2005 with WIPO Receiving Office. The rectification request filed on September 23, 2005 refers to page numbers as electronically filed. However, the Receiving Office has selectively entered the request, removed blank pages only and renumbered the pages in the application. As a result, the page numbers referred to in the previous request no longer match with the page numbers in the application that is wtfh EP-ISA. Accordingly, this request for tectification refers to only page numbers &at are current in the application forwarded to EP-ISA. This conawunication includes a substitute specification and substitute claims as per the EP-ISA recommendation. The corresponding page numbers in the substitute specification and claims are indicated in the rectification.

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Rectifications to PCT-SAFE Electronic Filing Errors

The applicants request the deletion of the blank spaces and formatting errors that were inadvertently introduced in the above referenced application during the PCT-SAFB electronic filing. The errors were obvious errors caused by defective conversion and transmittal of files and were not intended and shall he regarded as obvious errors in documents under PCT Rule 93.1(b), The rectification itself is obvious in the sense that anyone would immediately realize that nothing else could have been intended than what is offered as rectification. Accordingly, Applicants respectfully request time *mtry* of this correction.

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Rectifications to Typographical and Obvious Errors

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Applicant has rectified the specification and claims 1, 14 and 18. Support for the rectifications can be found throughout the specification and on, for example, page 20, lines 5-23; page 51; pages 57-59; pages 71-73; page 90; pages 106421; page 134, scheme 14; page 149, lines 26-31; page 150, Hnesl-4; page 156, lines 27-31; page 157, lines 1-10; page 161, lines 20-29; page 185, lines 25-31; page 186, lines 14; page 189, lines 11-25; and page 203. A substitute specification and substitute claims ate enclosed as per EPISA recommendation. No new matter has been added by this rectification.

10 The rectifications on pages 13, 15, 18, 22, 33, 35-37, 73, 79, 86, 98-1'00, 103, 106, 112, 113, 117*121, 150-152, 154, 156-158, 160, 169, 173, 176, 177, 186, 188,207, 225, 230 and 233 ate formal corrections to inadvertent and obvious typographical and formatting errors. Applicants respectfully request the $e\pi$ ty of this correction.

15 On page 15 of the specification as filed the -word "phenolic" was inadvertently omitted in the description of the term "hydroxyl-containing", which has been introduced by this rectification. Support for this rectification can be found thorough out the specification and particularly in structures I-H1-NOPD1, 1-HI-NOPD2a, I-HI-NOPD2b, and I-H1-NOPD3 on page 51; X-HH-MPDS on page 57; I-HH-MPPI 3 and I-HH-MPD15 on page 58; I-HH-MPM6 and I-HH-MPD17 on page 59; I-CH-MPD4 on page 63; and illustrative examples of NO-releafling prodrugs of Paracetamol on page 89 and Mesalamine on page 90 and of Vitamin E (alfa-tocopherol) on page 95. Applicants respectfully "Bubst the entry of this correction.

On page 15 of the specification as filed the term "cyclobutyP was inadvertently included in the definition of alkyl as "acyclic alkyl chain". Since the term "cyclobutyl" is a cyclic alkyl chain and not an acyclic alkyl chain, the said term is deleted from the definition of acyclic alkyl chain and is included appropriately under the definition of cyclic alkyl chain in the subsequent paragraph by this rectification. Applicants respectfully request the entry of this correction,

Oa page 38 of the specification as filed the structure I-CI-FDIO was inadvertently presented incorrectly. The experimental procedure for I-C1-PD10 described on pages 149-150, Example 12, in which SJM and cetirizi π e dxhydrochlo π de react, can yield only the compound having the structure of I-CJ-JtøtøO with apara-chloro phenyl group as presented by this rectification. Accordingly the coarect structure for I-C1-PD10 has been introduced on page 38 in the specification. Applicants respectfully request entry of this correction.

On page 40 of the specification as filed the product I-A1-PD18, described in the Example 32 on pages 156-157 was inadvertently omitted. The experimental procedure for I-A1-FD18 described on pages 156-157, Example 32, can yield only the compound having the structure of I-A1-P θ IS as presented in this rectification. Accordingly, Applicants respectfully request entry of Ms collection.

On page 44 and 215 of the specification as filed the structure I-H1-PD14 presented is an incoxxect structure and does rtot correspond to the description presented in the Example 3% on page t72. It is a duplication of structure I-H1-PD1 and is redundant, while the structure relevant to the Example 39 σ inadvertently omitted, The Example 39 on page 161 describes synthesis of I-H1-PD14, as shown in the scheme 14, method C, on page 134, using tibe starting material LI-2c.TFA (LI-2c in presence of trifluoroacetic add (TFA)) which has a BOC protected "NiF group, which after BOC removal, couples τ the ding derivative having a leaving group (LG) to form an amide derivative, the product I-H $\ddot{\iota}$.*PD14. Accordingly, the correct st τ current of X-H1-FD14 has been introduced on pages 44 and 22? (corresponding to page 15 for claims) (claim 14)- Accordingly, Applicants respectfully request entry of this collection.

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On page 49 of the specification and page 216 of claims, the structure of I-A1-NOPP6 was $irø_d$ vertently presented incorrectly. The experimental procedure for I-A1"NOPD6 des_c ribed on page 185-186, Example 105, iQwhich freshly generated formyl chloride of LI-Ib and ojncpiaaok react, can yield Oftly the compound having the structure of I-A1-WOPD6 with S=O group adjacent to be π imidawle and a "CHa" group adjacent to pyridine ring as

presented by this rectification. Accordingly, Applicants respectfully request entry of this correction.

On pages 51 and 217 of the specification as filed, the product, I-H1-NOPD11, described in the Example 117, was inadvertently omitted. The experimental procedure for I-H1-NOPDU described on page 189, Example 117, can yield only the compound having a structure of I-H1-NOPD11 as introduced by this rectification. Accordingly, Applicants respectfully request the entry of this correction.

On page 61 of the specification as filed, the structure of I-CA-MPD22 was an inadvertent repeat of I-CA-MPD5, while the correct structure was inadvertently omitted. The structure of I-CA-MPD22 presented in this rectification is the only possible product described in the Example 73 on page 174, in which nicotinyl chloride hydrochloride reacts with I-A1-PD8. Accordingly, Applicants respectfully request the entry of this correction.

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On pages 106, 119 and 121 of the specification as filed, the phrase "NO-releasing" was inadvertently introduced while combining the two priority provisional applications. The present application combines the subject matter of both the provisional applications and accordingly the invention is broader in scope than the invention presented in any individual provisional application. It is appropriate to use "compounds of formula I" or "prodrugs" in place of MO-releasing prodrugs". Support for the rectification is found throughout the specification and, for example, on page 23, lines 20-22 and in the list of candidate drugs on pages 106-120. Accordingly, Applicants respectfully request the entry of these corrections.

On page 173 of the specification as filed, the reactant used was inadvertently presented as I-S12-PD2, which should read "BOC deprotected I-S12-PD2." In fact, BOC containing I-S12-PD2 was deprotected to react with nicotinyl chloride to obtain the product I-CA-MPD18 in the Example 70. Accordingly, Applicants respectfully request the entry of

this correction.

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On page 197 of the specification as filed, inadvertently, erroneous ¹BNMR data was provided for **I-AX-NOPDtf** which is inconsistent with its structure. Accordingly, Applicants respectfully request the entry of this correction.

Claim 1 has been rectified to recite "or novel intermediates in preparation thereof, for which support can be found through out the specification and for example, pages 71-73*

Accordingly, Applicants respectfully request the entry of this correction.

No new matter feas bem added by this editorial rectification. Favorable consideration and entry of all the rectifications prior to publication is respectfully requested.

Respectfully submitted,

15 Dated: January 25, 2006

X_^__Vyu^uJvy

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25 Enclosure

Cc: ÏB WIPO

PRODRUGS CONTAINING NOVBt BIO-CLEAVABLE LINKERS

This application takes priority from US Provisional Application USSN: 60/604,632 filed 26 August 2004 and Indian Provisional Application 779MUM/200S filed 01 July 2005 and are herein incoiporated in their entirety.

Field of the Invention

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The present invention relates to compositions of prodrugs, including NO-releasing prodrugs, codrugs, double prodrugs and mutual prodrugs, containing bio-labifø linkers and linkages, processes for their preparation and pharmaceutical compositions containing them and fheir use

Background of the Invention

A prodrug is an active drug chemically transformed into a per sø inactive derivative which by virtue of chemical or enzymatic attack is converted to the parent drug within the body before or after reaching the site of action. The process of converting an active drug into inactive foitm is called drug latentiation. Prodrugs can be camer-linked-prodrugs and biopjecursofs. XKe carrier-linked prodrug xesults font a temporary linkage of the active molecule with a transport moiety. Such prodrugs are less active or inactive compared to the patent active drug. The transport moiety will be chosen for its non-toxicity and its ability to ensure the release of the active principle with efficient kinetics. Whereas the biOprecursors result from a molecular modification of the active principle itself by generation of a new molecule that is capable of being a substøte to the metabolizing enzymes releasing the active principle as a metabolite,

Prodrugs are prepared to alter the drug pharmacoikinetics, improve stability and solubility, decrease toxicity, increase specificity,, and increase duration of the phawnacological effect of the drag. By altering pharmacokinetics the drag bioavailability is increased by increasing absorption, distribution, biotransformation, and excretion of the drug. Limited intestinal absorption, distribution, fast metabolism, and toxicity are some of Hie causes of failure of drag candidates during development. Avoidance of trae foreseeable or proven pharmacokinetic defects thus assumes considerable significance in drug research. Accordingly, prodrugs play a significant role in drug research as well.

In designing the prodrugs, it is important to consider the following factors: a) the linkage between the earner and the drag is usually a covale π bond, b) the prodrug is inactive or less active than the active principle, c) the prodrug synthesis should not be expensive, d) the prodrug has to be reversible or too reversible derivative of the drug, and e) the carrier moiety must be nontoxic and inactive when released.

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Prodrugs are usually prepared by: a) formation of ester, hermesters, carbonate esters, nitrate esters, amides, hydroxamie acids, carbamates, iminea, maanich bases, and enamines of the active drug, b) functUmatøzing the drug with rø>, glycoside, peptide, and ether functional groups, c) use of polymers, salts, complexes, phosphoramides, acetals, heroïacetals, and ketal forms of the drug. For example, see Andrejus Korolkovas's, "Essentials of Medicinal Chemistry", pp. 97-118.

The discovery and characterization of endotøelium-derived nitric oxide (NO) was the subject of the 1998 Nobel *fti&s* in Medicine and Physiology. NO is a major signaling molecule with important biological roles. Sec, for example, Kerwja, Jr., J. F. et al., J. Med. Chenα 1995, 38, 4343, and Williams, R-J-P-, Chem. Soc Rev., 1996, 77. The major biological functions of NO include controlling blood pressure, smoothing muscle tone and inhibition of platelet adherence and aggregation* assisting the immune system in, destroying ttuftoj cells and intracellular pathogens and participating in neuronal synaptic transmission. See, for example,, Moacada, *S.* et al., Pharmacol. Rev. 1991, 43, 109; Bredt, P.S. et al., *tow.* Rev. Biocbem., 1994, 63, 175; Schmidt H. H-, W. et al., Cell 1994, 78, 919; Fóldman, F. L. et al., Chern. and Eng. News. 1993, 71 (20th December issue), 26; and Wilsonm E. K.* Otem. and Ettg. News. 2004 (S* March issue), 39. Endogenously, NO is produced from arginirte *by* the catalytic action of nitric oxide jrynüiase. See, for example, Nathan, C. et al., Celt 1994, 78, 915, and Marietta, M. A., Cell 1994, 78, 927.

NO is a firee radical as welt as a scavenger of free radicals. NO reacts quickly with ubiquitously generated reactive oxygen species (ROS) such as superoxide (Oaf) to generate a nefarious perojjynitrite (ONOO') molecule, which i\$ implicated in many human diseases such as diabetes, heart disease, Al2-ae\u00fcneks disease and multiple sclerosis. In this setting, NO is often viewed as pathogenic. However, the chemistry of NO can also be a significant factor in lessening the injury mediated by reactive oxygen species (ROS) and reactive nitrogen oxide species (RNOS), There is a relationship

between NO and oxidatioa, iutrosatton and nitration reactions.. A number of factors determine whether NO promotes, abates or interconnects these chemistries. See, for example, Espay, β_t aL, A chemical perspective on the interplay between, NO, reactive oxygen species, and reactive nitrogen oxide species, Ann N. Y. Acad. Sá 2002, 962, . 195.

Thus* by being a free radical^ along with the ability to scavenge other tree radicals, NO is placed k a pivotal regulatory position. Insight into these pathophysiological processes and signaling are highly relevant to develop therapeutics.

NO deficiency has been implicated in tine genesis and evolution, of several disease states. In patients with cardiovasculaf problems, the production of superoxide is increased and level or location of NO synthesis is disrupted thereby causing cellular dysfunction as a result of vasoconstriction of blood vessels, which can lead to, if prolonged, cell damage or death. Agents that act to maintain üß noimal balance between NO and superoxide in vascular endothelial cells may prove particularly useful in this regard, Sec, fbi example, Stokes, K., et BL, Free Radic. Bio. Med., 2002, 33, 1026-1036.

Nutritional and pharmacological therapies that enhance the bloactivity or production of NO have been shown to improve endothelium-dependent vasodilation, reduce symptoms, and, slow the progression of atherosclerosis. Some of the strategies for KO modulation encompass anti-inflammatory, sexual dysfinction, and cardiovascular indications. Apart from newly developed drugs, several commonly used cardiovascular drugs exert their beneficial action* at least in part, by modulating the NO pathway. Pharmacological compounds that release NO have been useful tools for efvaluating the pivotal role of NO in cardiovascular physiology and Hietapeutics,

NO-DONORS;

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There are a wide variety of structurally dissimilar organic compounds that act as NO donors and release NO in solution. Some NO donors, such as isoatnyl nitrite, troglycerine (GTN) and sodium nUroprusside, have been used in cardiovascular medicine long before their biochemical mechanism was understood. The common mode of action for these drugs is liberation of NO, which evokes relaxation of smooth muscle through activation of gualitate cyclase with subsequent formation of cGMP- The relative importance of enzymtrtic versus non-enzyjnatic pathways for NO release, the identity of

the actual NO-generating enzymes and the existence of competing metabolic events are additional important determinants of the different NO donor classes. Pharmacological compounds that release NO constitute two broad classes of compounds: those that release NO or one of its redox congeners spontaneously and those that requite enzymatic raetabolism.to generate NO. Sec, for example Igna π o, L. J. et al., Nitrite oxide donors and cardiovascular agents modulating the bioactivity of nitric oxide: an overview, Circ, Res. 2002, 90, 21-28.

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Nitroglyceri Te/glyceri C trinitrate (GTN) and compounds referred to as nitfovasodøators or NO donors are fiequently used in (he treatment of ischemic heart disease. The common mode of action for these drugs is liberation of NO, which evokes relaxation of smooth ntasefe through activation of guanylate cyclase with subsequent formation of -sGMF. However, early development of tolerance to nitrate therapy, particularly during acute myocardial jnfarctjion, has been the clinically significant drawback with OTN and some of the other available organic nitrates. This is a significant clinical problem and these exists a need for novel nitrate-based anti-anginal agents, which do not cause the problem of titrate tolerance.

There are a number of new examples of organic nitrates in which an alkyl or aralkyl mononitrate is covalently linked to an existing drug molecule, Existing drugs ftora a large number of therapeutic areas such as anti-inflammatory, antiallergic. antibiotic, anticancer, antidiabetic, antiviral, antihypertensive, antianginal, anticonvulsant, analgesic, antiasthmatic, antidepressant, antidiarrheal, antiarfedive, antimigraine, antipsychotic, antipyraiie, antLulcerarjye, antithrombotic, etc., were made and evaluated. Some of Nicox's patents include; Synthesis and evaluation of nitro Gxy derivatives of NSAIDs (WO 94*2463, WO 0230867, WO 0292072, WO 0313499 and WO 0384550), aspirin (WO 9716405, WO 0044705 and WO 0104082), paracetamol (WO 0U2584 and WO 0230866), antiepiteptic agenta (WO 0300642 and WO 0300643), COX-2 inhibitors (WO 0400781 and WO 0400300), statins (WO 04105754), ACE inhibitors (WO 04U0432 and WO 041063Q0), and of known drugs used for the treatment of disease conditions resulting from oxidative stress and endothelial dysfunction (WO 0061537).

Most of these nitrate esters were shown b possess not only superior or equal efficacy when compared to the original drug but also exhibit much-reduced side effects. In fact, because of fheir superior efficacy combined with reduced toxicity, a few of such nitrate ester-containing drug conjugates are successfully passing through various stages of clinical trials. Some of Nicox's nitrooxy derivatives of drugs which are in clinical trials include: NCX 4016 (Phase II, peripheral vascular diseases), NCX 701 (Phase H, Acute pain), HCT 1026 (Phase I, Alzheimer's disease), HCT 3012 (Phase II, Osteoarthritis), NCX 285 (JND, Osteoarthritis), NCX 1022 (Phase Ha completed, Dermatitis), NCX 1020 (Phase I, Asthma/COPD), NCX 1000 (Phase I, Portal hypertension), and NCX 1510 (Phase II, Allergic rhinitis).

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US5767134 and US20050002942A1 disclosed a few disulfide-contajirawg prodxugs/folatc-dtug conjugates. WO 9842661, US 5807847, WO 0054756 and WO 0149275 reported a few nhrooxy derivatives of organic molecules containing stdfahydryl or disulfide group which are called "SS-nittates". These references are incorporated herein by reference.

Representative examples from WO 9842661 have shown superior vasorelaxant activity and no tolerance was observed to the pGMP-*nciEas«]tg effects of those compounds wider Use same experimental conditions used for the induction of in vivo tolerance. WO 0J49275 reports drug conjugates where m. atti-inflammatory drug is covalently linked to the bea-Tonercapto-nittate via fhloester bond. Biotransformation pathways proposed for NO release from GTN bave largely been hemc~depeaden,t or sulfa Oydryl-dependent, See, for examples, Thatcher, G.R.J. et al., Chem.Soc. Rev. 1998, 27, 331 and reference cited thereto, and Bennett, B.M. et at, Trends Pharmacol, Sqi. 1994, 15, 245. These references ate incorporated hejcein by reference.

A mutual prodrug is the association In a unique molecule of two drugs, usually synergistic, attached to each other, one drag being the carrier for the other and vice versa. The embodiments of the invention also provide mutual prodrugs, which axe prodrugs of two or three therapeutic agents currently used/potential for use in combination Uxerapy utilizing novel bio-cleavable linkers, water-soluble prodrugs of iusoluble/spariiigly-soluble therapeutic agents using the same linker technology and water-soluble double and

triple prodrugs of sparingly-soluble therapeutic agents or any off the prodrugs linked to NO-releasing agent using the same linker technology.

Summary of the Invention

Present invention relates to $ffe\beta$ compounds of forwula (J) or pharmaceutically acceptable salts tfccreof;

$$D^{1}$$
 E
 A
 B
 A^{1}
 E
 C
 E
 A^{1}
 B
 A
 E
 A
 E
 A
 D^{2}
Formula (I)

wherein,

a is 0-2;

B iπdep« Od« Ody represents a bond, (CHjQb, (CH₂CHzO)«, S-S, S-SK) ₁ S-SO ₁ or S-S=NHj b is 1-6; c is MOOO;

A and A¹ independently represent a bond, (CHa)* 1,2-pheOytene, $l\beta$ -pbmyle>nE or 1,4* phenytene;

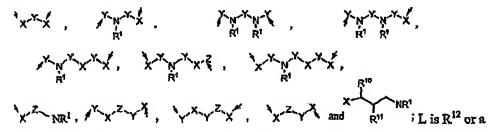
d is 1-8;

D¹ jepiesents a therapeutic agent comprising one or more of the fiw/Tetkmal groups selected fown the group cojisisti Ogof -OH, -SH, -NHR¹, -CO₂H, -CONHR¹, -OCC-O)NHR¹, -SOiNHR¹, -OSO₂NHR¹, -N(R¹)C(-O)NHR¹ and -N(R¹)Sθ2NHR¹; D^a independently represents D¹, a peptide, ptoteio, Atonoclons i antibody, vitamin, R\R³, R⁴_SNO, Nθ₂₅ a linkable nitric o Kide-c βeasing group comprising a NONOste, a group comprising one or more of ivater-solubilizing ftraetSonal groups,, ot a polymer;

comprising one of more of trater-solubnizing fractisonal groups,, or a pos

E ifldepettdently t&resents CEa or a bond;

 L^1 and L^3 independently lEpieses α a bond, O_1 S, NR^1 , L, or a linkage selected from the group consisting of:



25 group with bonding in any direction independently selected from &e group consisting oft

- 5 X independently represents a bond, C, O, S, or NR¹;
 - Y independently represents a bond, C=O, C=S, S=O, SO2, P(=0)XR¹, or (CH2)d;
 - Z independently represents a bond, or (CH2); wherein, j is 1-4;
 - R1 independently represents a bond, H, (C1-C8) alkyl, (C5-C14) aryl, aralkyl or Me+;
 - R² independently represents H, NH₂, or NHAc;
- 10 R³ independently represents H, CO₂R⁵, CH₂CO₂R⁵.
 - R^4 independently represents H, OH, O-(C₁-C₀)alkyl, OM⁴⁺, or a group selected from the group consisting of:

M mdfepeiideotily represents Na, K or a pha π naceutically acceptable metal ion, e = 1-3,

R⁵ independently r&ptesente at each occurrence H, M¹, (Ci-Cs)alkyl, (C3-Cg)oyclo-ilkyl, substituted (Cs-C_M)aiyl, het«ro(C₂-C)L4)alyll, CC⁰OJCC¹CHR⁰CO¹, CHjC(⁰O)OR⁵, P(=O)(OR⁵)₂,

 X^2 mdependetttly r^>reseats $O_a S$, SO, SO^, or NR⁵;

 R^{β} independently lepneseats $H_{\Lambda}Na^+, K^+$, any other phaimaceutjeaUy acceptable metal ion,

10 (CrCgJalkyl . or (Q-CiOcyeloatkyl,

 $R^{7} \ \text{independently represents} \ \text{ at each occurrence } \ \text{ same or different } \ R^{5};$

R8 independently represents CH2, 0, NR4»S₅S=O or O=S=O;

R? independently represents H, (Ct-Cg)alkyt or aft amino acid;

£ is 0-6;

15 g is 0-1;

Ii is 1-2000;

i is 1-4;

R waad R J i indepejadeat $\ddot{i}y$ fEptresent H, {Ci-C^alkyl, (C₃-Q)cydoalfcy \ddot{i} - or a group selected from the group consistky of:

With a proviso that when R^{10} is selected from the above group, R^n represents H or (Cj-C₈)alkyl, and when R^{11} is selected from the above group, R^{10} represents H ot (Ci-

5 C₈)aftyl;

 $R^{\,!\,2}$ independently represents a group selected from tha group consisting of;

and X3 is independently O or NR7.

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Another embodiment of the invention is a pharmaceutical composition comprising one or more compounds of formula I or intermediates thereof and one or

more of phatmaceutically acceptable carriers, vehicles oi diluents. Further embodiments include methods of preparation and methods of use of prodrugs including NOrelcasing prodrugs, double prodrugs and mutual prodrugs comprising the compounds of formula I itteta Üeij Description of the Invention

The present invention characterizes compositions, methods of preparation and methods of use of prodrugs, NOreleasing prodrugs, mutual prodrugs, double prodrugs, arxd eodrugs.

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The compounds of the present invention are prodrugs or mutual prodrugs in which known therapeutic agents or potential therapeutic agents are linked covaleøtiy to novel Wocleavable linkers.

Toe compounds of the present invention also include NO*teleasing prodrugs in v)Ho)x a therapeutic agent is linked covalently to nitrooxy (nitrate ester) group via a novel bio-cteavable linker containing a strategically placed disulfide group at β -position to the nitrate ester. The present invention also characterizes composition of NO-releasing prodrugs (Le., nitrooxy ester or nitrate ester prodrugs), processes for their preparation, pharmaceutical composition containing them and their use.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as coxrøConly understood by one of ordinary skill in the art to røfcich this invention belongs. Listed below are definitions of various terras used to describe the compounds of føe present invention. These definitions apply to the term as they are vised. throughout the specification (unless they are otherwise limited in specific instances) either individually or part of a larger group.

The term "amino-contaitting" refers to drug/carrier molecule wth NH functional groups such as amino (both primary and secondary), amide^ urea, sulfonamide, carbamate, phosphoramadite, isulfamate, hydrazone, sepitcatbazone, thioserøjcarbazone, hydrazide, catbazate and the like. This also includes NHK;oD.taining hetarocylic compounds such as imidazoles, benzitti idazoles, pyrazoles, benagpyraszoK pyrrols, indoles, friaz des, tetrazoles, benzotriazotes, benzotetrazoles and titeiic derivatives. These NH-containing heterocyclic compounds can be sub-structures of more complex drug/camer molecules. Amino group of the candidate drug can be primary or secondary

(both acyclic and cyclic) which include amide-NH, \$uifona_tnde-"NH, carbatnate-NH, sulfamate- NH, hydrøide-NH, hydrazone-NH, semicarbazone-NH, thiosemicarbazone-NH₅ urea-NH and also drugs containing indole, imidazole, beazimidaaole, tbjaz **G**c, oxozøle, pyrrole, pyrøzole, triazole, tetrazole, or similar >JH-contajnix}g heterocylic substructures of a more complex drug molecule,

The term "liydroxyl-ooiitaii Úng" refers to dnig/camer molecules witt hydrøxyl groups (priraary, secondary, tertiary and phenolic) including hydroxyl groups of hydroxsmic acids and ketoximes derived from fceto-containing molecules. Hydioxyl group of drugs can be of primary, secondary, tertiaiy or phenolic nature.

The tejm *'s«l^diy Ï-co»taH«ng" refers to ojugtesffter -with ftee sujfahydtyl (SH) group.

The tenn "halo" refers to fluoro, chloro, biomo, and iodo.

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The teø π "Mid β ' refers to fluoride, chloride, twomid β and iodide.

The term "afisyF refers to acyclic allsyl chains. For example, fke term "Ci-Ce alkyr i δ fexs to $m\phi$?" ethyl* propyl, isopropyL, butyl, s-butyl, and t-butyk peitfyl* tesyl, hepiyl, octyl, and the like.

The teen "cycloalkyr ircfers to cyclic alky" chains, βg , t3be tero " $C_3 - C_8$ oycloalky" refers 'to cyclopfopyl, cyclobutyl, cycloodyl, cyclopentyl, cydohcxyl, β ycloheptyl; cyclooctyl and the like.

The tesoa "atyl" refers to phenyl^ Üaphtiiyl and the Eke.

The term "aralkyP refers to fceilzyi, ph hethyl and fitc like.

The term "alkoxy" $\neq tets$ to bofli acyclic and cyclic Ci-C₈ alkyloxy *For example, the te π n " C_1 - C_9 aliyloxy" refers to $methoxy_>$ ethoxy, ptopoxy, isopiopoxy, cyclopropoxy, butoxy, cyclobutoxy, s-birtoxy;, and t-b Uoxy, cyclope $\hat{\mathbf{T}}$ yloxy, pentyloxy, hexyloxy, cyclohexyloxy, S^ptyloxy, cycloheptyloxy, octyloxy^ cyclooclyloxy and the like.

The term "heterocyclic" and "heteroaryr refers to both saturated and tmsat Otated 5- and 6-merabe)red rings (including benzo-Jfased) containing from I to 4 heteroatoms selected from the group 'consisting qf nitrogen, oxygøtt aiid sulfur. AU of these rings may be substituted with Up to three substitutents independently selected from toe group

consisting of amino, halo, alkoxy, alkyl, cyano, oitro, hydrøxyl, sulfahydryl, carboxyl a»d the like. Saturated rings include, for example, pyrrolidine, pjperidinyi, pipexaziπyl, tetrahydrofuryl, oxaz didjnyl, dtøxanyX, pyranyl, and the Mice. Beftzofused saturated rings include iodolinylj 1,2,3,4-tetrahydroqui ποΗnyl, 1,2,3,4-tetrahy dbisoqmnoli πyl and the like. Unsaturated rings include fiiryl, thtøayl, pyridinyk pytrolyl, N-JtOethylpyrrolyl, oxazolyl, isoX-tzOlyl, pyrazolyl, imidazoty], tetrazolyl, triazolyl, oxadiazolyl, thiadtazolyl, ftuazolyl, pyrimidinyl, pyrazinyl, pyridazi πyl, and the like. Beπzoiused unsaturated rings include jsoquino ïwiyl, besrc&ox Ozoiyl, benzthiazolyl, qianolinyl j benzofura Oylj thionaphthyl, indolyl and the like.

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The term "substituted alkyl" refers to acylic and cyclic all&l groups substituted with owe or more of groups such as alkyl, aryï, hydroxy, allsoxy, cysno, carboxyl, sulfahydryl, alkyltMo, amino, nitro, halo, carbonyl, carbamato, sulfamato, su

The term "substituted aiyF refers b aryl groups substituted (including fused) with one or more of groups suck agalkyl, aryl, hydroxy, alkoxy, cyano, carbo^yl, sulfahydryl, alkylthio "amino, nitto, halo, carbonyl, caibamato, sul&mato, suUfemto, sulfate, and the like.

The term "amino acid" refers b molecules containing one or more amino and carboxyl groups. Examples of sffa-amhrø acids (D_n , L- and DL- amino acids) -include natural alanine, argiaia β , asparagine, aspactie acid, cysteine, glutamic acid, glutamiiRe, glycine, htstidtae* isoleucine, leucine, ïysi π e, methionine, phenylalanine, proline, serine, thre σ kine β tryptophan, tyrosine, and valine. Other examples include beta-atnino acids and known ttnOaturaL amino acids.

The text "amino add ester" as used in this specification refers to an amino acid where the Caxboxy group is substituted with a Cj-Cg alkyl group. That is 5 to all cyi group when taken together with the carboxyl group foims a Cj-C« alkyl ester- It is appreciated that some amino acids (eg., aspartic acid and glutamic acid) have two carboxyl groups these may form mono- and digesters.

The term "protecting group" (PG) refers to an 'amino protecting group' or a 'hydroxy! protecting group' or a 'carboxyl protecting group' and the like.

Hie term "amino protecting group" refers to a group that selectively blocks or protects the amino flinctwoality in presence of other functional groups on the molecule. Examples of such amino-jiroteotrag groups include tire-formyl group, the triiyl group, the phthaHoudo group, the acetyl group, the trifluoroaceiyl group, the chloroacetyl^ ajjd iodoacetyl groups, viethane-type blocjdng bromoacetyl, groups such 9-fluore πylmetli.oχycarbonyl benzyloxycarbonyl ("CBZ"), ("FMOC"), featbutoxycarb cayl ("BOC"), tricHorocthylcarbonyl and the like. Additional examples of amino protecting groups ate described by T, W. Greets "Protective Groups ta Organic Synthesis", John Wiley and Sons, New York, NX, 1991. Molecules with two or more amino groups may form mono-, di», tri-, poly-, protected derivatives depending on flic reaction conditions used.

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The term "hydroxyl protecting group" refers to a group that selectively blocks or protects hydroxy! tonctionality in presence of other reactive fiffictional groups on the molecule. Examples of such hydroχÿi-protectfcg groups include, for example, ether groups including methyl and substituted methyl ether groups such as methyl ether, methoxymethyl ether, mefhylthiorøefhyl ether. tert-buy ithioroβthyt ether. tήphβαylmetiiyl, tdmhydropurattyl (THP), (phenyldim βthylsïlyl)meflh05(y-methyl ether, bβnzyloxymethyl ether, p-meihoxybenzyloxy-incfliyl ether, and teat-butoxymethyl eiherj substituted efb.yl βthw groups such as eihoxyethyl ether, l-(2-chtoroet-røty)-ethy)t e&er, 2,2\(^-\tridhlo\) roetlioxyroethyl cttier> and 2-\(\tri\) (triω \(\text{w}\) \(\text{tgl}\))ethyl eth\(\text{w}\); isopfopyl ether groups; phenyl and substituted phenyl ether groups such as phenyl ether, p-chlorophenyl ether, p-methoxyphenyl ether, and 2,4-dMfrop]ieray ether, benzyl and substituted benzyl ether groups such as benzyl ether, p-methoxybenzyl ether, o-nitrobenzyl ether, and 2,6dibhlorobeni (yl ether; and alfeykdlyi ether groups such as foimethyi-, taethyl- and tmsopropyisttyl ethers, mixed alkylsilyl ether groups such as diniethylisopropylsilyl ether, tert-butyldi methyls \u03c4yl ether and diethylisopropylsilyl ether; and ester protecting groups such as acetate ester, formate ester, benzylfocmate ester, mono-, di-, and ttichloroacetate esters, pivalate ester, phetrøtyacetate ester, and p-chloroplienoxyacetate, benzyloxycarbonat B, 9-jQuoi«nylttteflio?[ycarbonate, tert-butoxycarbonate, triohloroethylcaibonate, carbamate, sulfonate and the like. Additional examples of hydroxyl protecting groups are described by T, W. Greene, "Pfot«cfave Groups in

Organic Synthesis", John Wiley and Sons, New York, NT-, 1991. Molecules with two or more hydroxy! groups may form mono- and di-esters/ethers depending on the reaction condition,

The term "carboxyl protecting group" refers to a group' that selectively blocks or protects carboxyl ftinctionality in presence of ofe reactive functional groups ou the molecule. Examples of such carboxyl-protecting groups include, for example (substituted) alkyl esters such metjbyj ester, ethyl ester, t-butyl ester, (substituted) benzyl ester, trichloroethyl ester, and the like. Additional examples of carboxylic acid protecting groups are described by T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons New York, N.Y-, 1991. Molecules witø, (wo or more carboxyh'c acid gtoups may førra mono, di-, tti-, tetTa-5 poly- protected derivatives depending upon the reaction conditions used.

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The term "carboxyl activating group" refers to leaving group ("LG") of a carboxyl derivative that js easily replaced by an focomkg nucleophile. g^dj "LG" groups include, but are not limited to, (substituted) alkoxy, acyloxy_a nitrogen containing unsaturated h β ejocyctes such as N-oxybe π zotriazole, imidazolyl, o/p-rtitrophenoxy, pentacbio iophenoxy, N-oxysuccin ω N^N*-dicycloh β kylisou Ta-O-yl, N-itydroxy-N-methoxyamino, and the like; acetates, formates, sulfonates such as rø-thanesulfouate, β han β si-Ifonate, benzeflesulfonat β or p-toluenesul&itiate, and the like; and halides especially fluoride, chloride, bromide, or iodide.

The tenth "carbonyl activating reagettt" j few b a reagent "ttiat converts the earbonyl of a carboxylic acid group into one th# is mote susceptible b nocl fephilic attack and includes, but is not limited to, such reagents as those found in "The Peptides", Gross and Mdcnhofer > Eds.» Academic Press (1979),. Ch. 2- and M. Bodanszky^ "Principles of Peptide Synthesis", 2,sup,nd Ed. > Spriflger-Veriag Berlin Heidelberg, 1993, hereafter xeferred b as "The Peptides" and "Peptide Synthesis" respectively. Carbonyl group (i.e., aldehyde or leeto group) of candidate drugs may be converted first b aldoxirae, krtojtfme, hydrazone, seiuicarbazone and lire like, before coupling to the linker. Specifically, carbonyl activating reagents include thionyl btomide, thionyl chloride, oxalyl chloride, and the like; esters of alcohols sue)* as nitrophenol, pentachlorophenol^ and -the like; and compounds such as l^--carbonyldiimidazole (CDI),

bcOkotriazole, imidazole, N-hydroxysuccinimide, dicyclohexylcarbod&nide Ψ CC% EDC₃ phosgene or its equivalents, N, N-dimethylaminopyridme (DMAP) and the like.

The terms "phosgene or its equivalents" refer to phosgene or it equivalents such as diph Gene, triphosgene, CDI, PSC, BTBC, alkoxycaibonyl chlorides* o/p-Ritrosubstinited phenoxycarbottylchlorid.es, and the like.

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In general, the term "phairaao Butical" when used as an adjective means substantially non-toxic to living organisms.

The terms "pharmaceutically acceptable metal ions or salts" refer to salts of the compounds of this invention, which are substantially non-toxic to living onanisms. Sec, e.g., Berge, S, M. et al, "Pharøtaceutical Salts", J. Phaem. SGL, 66:1, 1977. Typical pharmaceutical salts include those salts prepared by reaction of the compounds of this ittve&ttan with an inorganic or organic acid or base. Such salts are known as acid addition or base addition salts respectively. These pharmaceutical salts f Equently have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions. Examples of pharmaceutically acceptable salts are those with inorganic bases such as sødiux π , potassium, calciums magnesium, and hydroxides, and the like, or with organic bases such as lysine, arginine, tnethylamine, dibtnsylainme, piperidine, and the like.

The term "suitable solvent" refers to a solvent fliat is inert to the ongoing reaction m $\acute{\alpha}$ sufficiently collisizes the xeactants to effect the desired reaction. Examples of suitable solvents include hxst are not limited to dicMoromethanc» chloroform, 1,2-dichlotoetbane, dietiiyl etheiv tert-butyhnethyl ether, acetonitcfle, ethyl acetate, 1,3-dimethyl-2-iHiida2 θ lidinone, tetrahydrofuran, dinnethylfow π amide, benzene, tolueHc, xylene, N-diraethyHacetamide, N-methylpyil otid-ne, chlor Chenziene, dimethylsulfoxide, diroethoxyethane, -water, "methanol, ethanol, isopropanol, pyridine, ratroincthane, mixtures theieofe and the like.

The teim "suitable base" refers to a base, which acts as a proton trap for any protons, which may be produced as a byproduct of the desired reaction, or to a base, which provides a xevetsible deprotonation of an acidic proton from the substtate and is reactive eaough to effect the desired reaction without significantly effecting any undesired enactions. Examples of such bases include^ but are not limited to, carbonates,

bicarbtmates, and hydroxides (e.g., lithium, sodium, potassium, magnesium, calcium, and tile like), sodiuin/pot-usiuHi/calcium, hydride, sod $\ddot{\mathbf{U}}$ -EQ/potassium alkoxide (i.e., tnethoxide, athoxide, tert-birtoxide and the like), tri β iiylaini α , dusopropylethylaraiae, N-me&ylpyrtoHdia β , N-methylinoipboHm, , tetramethylguitiiditie, or aronnatic nitrogen containing heterocyctes such pyridine, 4-(d3methylamino)pyridij]ie (DMAP), and the like.

The tefjQ "NQNOat β ' refers to a linkable nitric oxide-releasing group such as AcOCJHbQ-Na-N(Cr)R⁷, OCHOCH₂-O-NrN(OO R⁷R⁷, CH₂-O-N₂-N(O^R R⁷ and the like.

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The term 'htherapeutic agent" refers to biologically active molecules such as drugs, vitamins, and other molecules, agents or substances concerned with or attributing to the treatment and cure of illness ot contiibiting to the general well being of a mammal or human. The therapeutic agents can he both known and investigational drugs compiled in drag databases such as the Mctck Index, IDdb, Prous Science's Integrity®-Prous Science Drugs of the FutureTM, The Ecsejntøe® and tø.e like. The Merck Index is a one-volwmc encyclopedia of chemicals, drugs and biologicals that contains more than 10,000 monographs. Each monograph ia this authoritative reference source is a concise description of a single substance or a small group of closely related compounds. Prous Science is an international health science publishing company, established in 1958 and hcadqparteted in Barcelona* Spain. Prøus Science Drugs of the Futox βM, produced by Prous Science Publishers, contains compwhrøsrve dtug monographs providing product inJSbnnatio T on new coropwnds, including the synthesis and corresponding schemes, pharmacological action, pharmacokinetics and mdabolism toxicity, clinical studies, mair@fectttret, and lef β rences. info π oation on compounds is continuously updated as advances in development status are disclosed worldwide. The Pious Science Integrity^ is a drug R&D portal where knowledge areas are coordinated to provide a haimonious and interrelated whole, which includes Prugs & Biologies, Targets, Organic Synthesis, BxperixnesHtal Pharmacology, Pharmacokinetics and Metabolism, Clinical Studies, " Disease Briefløgs, Companies & Markets, Uteri-tote and Patents. TTic investigational Drugs database QDdb), developed by Thomsoa Cmrent Drugs, is a pharmaceutic^ competitor intelligence service, It covers all aspects of investigational drug development, from first patent to eventual teunch ox discontinuation. The Ensemble® on the Web

provides essential information, including chemical structures, on more than 140,000 compounds with demonstrated biological activity in the drug research and development pipeline.

The term "vitamin" includes vitamin A, vitamin C, thiamine,, folio acid, biotm, inositol, nicotinic acid, nicotinamide, riboflavin, pyrido me, jpyridoxal 5-phosphate, ergosterol. vitamin D2, vitamin D3, vitamin D4, vitamin E, menadoxirae,, mejnadiol, and vitamin K5.

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The term "peptide" includes large a Od small peptides, unctød ing, but not limited to, targetable small peptides such as a dipeptida, terpeptida, tetrapeptide, etc,

The term "ligaad" means a small molecule that binds to a larger macromple α ile, whether of not tfie ligaad actually binds at a metal site. Such ligands can be small peptides.

One aspect of the invention is to provide mutual prodrugs of two or three therapeutic agents cutrently used for use in combination therapy utilizing novel biocleavable linkers, water-soluble prodrugs of insoluble and sparingly-soluble therapeutic agents using the same linker technology, and -water-soluble double and triple prodrugs of sparingly-soluble therapeutic agents using the same linker technology. The embodiments of the invention may also comprise vitamins and targetable small peptides in addition to or 3 place of a prom Geity by ield targetable prodrugs.

The candidate drugs selected fox mutual prodrug synthesis cm be ftoRx one flierap&utic category Q from differe&t therapeutic categories. Similarly, the constituent drugs of a mutual prodrug can act on the same biological target with similar mechanism of action or act on different biological targets with different mechanisms of action.

To be considered for prodrug synthesis, tine candidate drugs should contain one or more of the essential functional groups such as amino, hydroxy!, fceto, or carbojtyl groups io their structure.

Axino group of the candidate drug cam be primary or secondary (both acyclic and cyclic) which iftetøde amide-NH, sulfonamide-NH, carbamate-NH, sulfemate-NH, hydfazone-NH, semicarbazone-lvJH, ariosemcajbazone-NH and also drugs cojrt^nmg indole, imidazole, benzimldazole, tfciazofø ojtozole, pyrrole, pyrazole, triazole, tetrazole, or similar NH-conti tiofog heterocylic substructures of a more complex drug molecule.

Similarly, hydroxyl group of drugs can be of primary, secondary or thatiaiy nature. Keto group of candidate drugs may be converted first to ketoxime, hydrazine, semicarbazoiie and the like, before coupling b the linker. Obviously-, hydroxyl or amino functions thus generated will be used to form covalent bond between the drug and the linker.

The candidates for nw&ing mutual prodrugs can be the pairs of drugs that are currently used in combination therapy (mcludittg those combination studies at investigational stage) in various therapeutic areas provided each of tiiose drugs possesses the requisite functional group(s). There are a number of therapeutic areas where such combination th&rapy is applied joutinely and successfully,

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On the basis of the proposed sulfahydjyl-depencient mechanism of NO-release from GTN₃ we have designed the compounds and prodrugs of the present invention where a suitable drug molecule is linked covalently to a wtrooxy (nittate ester) gfcoup via a Mo-labile linker containing strategically located disulfide bond at ^ef&position to nitrate ester. In vivo, the disulfide bond itx the prodrug is expected to be reduced by endogenous suifahydryl-confeaning species such as glutathione (GSH) b generate a, reactive thiolate anion (Le., δ gtø-mercapto» β it τ ate), which can trigger further break-down of the linker moiety to release the ftee drug (via a mechanism as shown Scheme MI) and NO simultaneously at the same location. It is possible, as depicted in the mechanism Scheme MJ, the release of MO can go via a hypothetical cyclic flatrøtønt intermediate 'b\ Similar hypothetical mechanism was proposed for MO release from SS-aitiatcs, ^hich weace also designed on Uie basis of a sulfahydtyl-dependentNO release from GTN. See, fox example, Zavorin, S. I et _L, Organic Letters, 2001, 3, U 13, kcorporated herein in its entire, y. Mutual prodrugs can be made by linking covalently any two of the following: an fpiino-containing therapeutic agent to another aniino-coj amning therapeutic agent; an amino-contafni Tg therapeutic agent to a hydroxyl-containing therapeutic agent; an aminocontai nttg tiierapeutic agent b a carbox^l-contatning thejapeutio agent and its derivative; a hydroxyl-c αotaining therapeutic agent to a carbo^yJ-eontaiott-g therapeutic agent and its derivative; an amiso-co maining therapeutic agent to a caiboxyl-contalning therapeutte agent and its derivative; an amioo-csojitaini-Tig therapeutic agent to a keto-contaming therapeutic agent or its fcydazone, semfcaibazone or oxime dexivative and the like; a

hydroxyl-contaittiag therapeutic agent to a ^-containing therapeutic agent via its hydrazoae, sejonicarbazone, or oxime derivative and the like.

Another aspect of the present invention is to provide jiew nitrate ester (NO releasing) prodrugs of many types of existing drugs using novel biodeavable. Ulcers. Such prodrugs are expected to exhibit better efficacy and tolerabiUty with reduced side effects compared to the corresponding original drugs.

An embodiment of present invention relates to the compounds of formula (I) or pharmaceutically acceptable salts thereof:

$$D^{1} \stackrel{L^{1}}{=} A \stackrel{A}{=} A^{1} \stackrel{L^{2}}{=} D^{2}$$
Formula (1)

wherein,

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a is 0-2;

B Mepettdently represents a bond, (CH₃)_b, (CHaCH₂O)₆, S-S, S-S=O, S-SO₂ or S-S=NH; bis 1-6; c is M 000;

A and A 1 independently represent a bond, ($CR\dot{o}$ \dot{q} \ddot{i} ,2-phenylene, 1,3-jpihenylene or 1,4-phenylene;

d is 1-8;

D*represents a therapeutic agent comprising one or more of the functional groups selected firøn tjie group consisting of -OH, -SB, -KHR.\frac{1}{2}, -CO_2H, -C0NHR \frac{1}{2} >> -OCC=O)NHR\frac{1}{2}, ^SO_2NHR\frac{1}{2}, -OSO_2NHR\frac{1}{2}, -N^CC^M \quad \text{i'} R^1 \text{ and -N(R \frac{1}{2}SO_2NHR \frac{1}{2}; D^2 \text{ independently represented D^1, apaptide, protein, monoclonal antibody, vitamicv R^z, R^3, R*,NO, NO_2... a linkable nitric oxide-releasing group comprising a NONOate, a group

25 comprising one or naore of water-solubilizing f ωctional grotips, or a polymer;

E independently represents CHk of a bond;

L 1 and }} independently represent a bond, O, S, NR 1, L, or a linkage selected &om the group consisting of:

L is R¹² or a group with bonding in any direction, independently selected from the group consisting of:

- 5 X independently represents a bond, C, O, S, or NR¹;
 - Y independently represents a bond, C=O, C=S, S=O, SO2, P(=O)XR1, or (CH2)d;
 - Z independently represents a bond, or (CH2); wherein, j is 1-4;
 - R1 independently represents a bond, H, (C1-C8) alkyl, (C5-C14) aryl, aralkyl or Me+;
 - R² independently represents H, NH₂, or NHAc;
- 10 R³ independently represents H₂ CO₂R⁵, CH₂CO₂R⁵,
 - R⁴ independently represents H, OH, O-(C₁-C₂)alkyl, OM^{2,}, or a group selected from the group consisting of:

$$CO_{2}R^{6}, CH_{2}CO_{2}R^{6}, CH_{2}CO_{2}R^{6}, CH_{2}CO_{2}R^{6}, CO_{2}R^{6}, CO_{2}R^{6}$$

M independently represents Na, K or a pharmaceutically acceptable metal ion, e = 1-3,

R⁵ independently represents at each occurrence H, M^{e+}, (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, substituted (C₅-C₁₄)aryl, hetero(C₂-C₁₄)aryl, C(=0)(CH₂)₂CHR⁹CO₂R⁵, CH₂C(=0)OR⁵, P(=0)(OR⁵)₂,

$$CH_2$$
-Dextran, CH_2 CO₂R⁶, CH_2 CO₂R⁶, CH_2 -Dextran, CH_2 -Dextran, CH_2 -Dextran, CH_2 -Dextran

X² independently tepresenis O, S, SO, SO₂, O NR⁵;

 R^6 to &pe Otlently represents H, Na^+ , K^- , any other pha $\pi\pi$ acceutically acceptable meta \ddot{i} ion,

10 (Ci-C₈)aUζl₈ or(C₇, C₈)βycloalkyl»

 R^7 independently rspr β seats at each occutrence same αt differ $\alpha C R^s$;

R⁸ jndependeoUy represents CH₂*O, NR⁴, S, SO or O=SK);

R⁵ independently tepresentsH, (Cj-C₃)alkyJ or acti amino add;

f is 0-6;

15 g is 0-1;

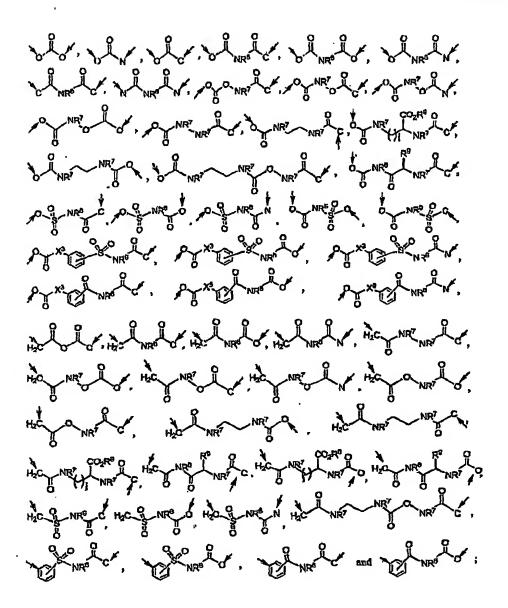
h is 1-2000;

Jis 1-4;

R IV d R n iadepcadettly represent H, (CVC^alkyl, $< c_3 - c_8$)cydoalkyl, or a group selected from the group consisting of:

with a proviso that when R^{10} is selected from the above group, R^{11} represents H or (C₁-C₈)alkyl, and when R^{11} is selected from the above group, R^{10} represents H or (C₁-C₈)alkyl;

5 R¹² independently represents a group selected from the group consisting of:



X3 is independently O or NR?

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D¹ and D² of the present invention can be both known and investigational drugs compiled in drug databases such as the Merck Index, IDdb, Prous Science's Integrity[®],

Prous Science Drugs of the FutureTM, The Ensemble[®] and the like. In a double prodrug, D^J and D² are Ü&same drugs. In a mutual prodrug, P^I and D² are different drugs. In some prodrugs, only DI is a drug and D² may not be a drug at all. Hie -OH, -SH, »NH₂, -NHR ¹, ^CQ₂H, -CONHR ¹, -OC(O)NHR ¹, -SOaNHR ¹, -OSO₂NHR ¹, -N(R^CC=O)NBR* and -N(R ¹JSOaHHR ¹ fottettoiud groups in D ¹ and D ² of formula I participate in the formation of linkages between the drug and the linker. Accordingly, some of the atoms or groups in L ¹ and L ² may come from the corresponding D ¹, D² or linker.

Another embodiment of the invention is the compound of formula I, wherein D^2 is an amino-, carboxyl- O bydroxyl- containing group or molecule comprising one or more water solubilizing functional groups selected from the group consisting of hydroxyl, amino, acylaminO, carboxyl, sulphate, sttffonata, phosphate, phosphoaajs, N-acylsujtfoftamide., N-acylsalfamate, N-acylcarbamate, N-aoylcarbamate metallic salts, and amino acids to give water-soluble prodrug.

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Another embodiment of the inveritfor is tfce compound of formula I, wherein D² is selected from the group of D, L and DL ammo acids coasiistiag of Alanine, Atginifte., Asparagine, Aspartic acid, Cysteine, Gtoteowne, Glutamic acid, Glycine, Histidine, Isoleucine, Leucine[^] Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, and Valine.

Anofiter embodiment of the invention is the coropowid of formula 1, wherein *P* represents a polymer selected from the group consisting of aiabinogalactan, polyamvno acids, polyethylene glycoj, polycapiolactone, polyglyooUc acid, polylactJc acid, polyacryKc acid, poly(2-hydroxyethyl 1-gtutaminft), dextran and modified dextrans such as dejttran aldehyde, carboxymethyl dexuan, arabinogalactane aldehyde,, carboxyn.eth.yl axabiaogalβctaiæ, and hyaluronic acid.

Yet another embodiment of the invention is the csompound of fowiwila I, wherein D² is a polyaiainoac id selected from group consisting of poly(l-glutamic acid), poly(d-gUitamic acid), poly(dl-ghit-uttic acid), poly(l-aspartic acid), poly(d-ag)artic acid), poly(dl-aspartic acid), copolymers of the polyaminoacids and polyethylene glycol,

Another embodiment of the invention is Una compound of formula I, wherein the polymer has a molecular weight of about 5000 to about 100,000 Paltona. Yet another

embodiment of the invention is the compound of formula %wherein, the polymer has a molecular weight of about 10,000 to about 50,000 Daltons.

It a further embodiment D^2 is a peptide, protein or monoclonal antibody for achieving targeted delivery of prodrugs and drags. Another embodiment of the invention is the compound of formula I, wherein D^2 is a liga πd or dipeptide or a dipeptide ligand. In a rurther embodiment D^2 is a dipeptide Ugand that is a substrate for intestinal transporters for selective intestinal absorption of the corresponding prodrugs thereby 'increasing the bioavailability of the prodrugs. In a farther embodiment D^* is a tatgetable small peptide, Sue., dipeptide, tripept ide, tetrapeptide, etc.

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Another embodiment of the invention is the compound of formula I, wherein O^I is a vitamin. Such vitamin-conjugated prodrugs at expected to be taken up by U*e diseased cells via receptor-mediated endocyt Osis. In a fiitthar embodiment of the invention is a cOtnpow Od of formula I, whetein, D^I is selected from the group of vitamins consisting of vitamin A, vitamin C, thiamine, folic acid, biotin, inositol, nicotinic acid, nicotinamide, riboflavin, pyridoxin pyridoxal 5-pb.osphate, ergosterol, vitamin D2, vitamin D3. vitamin D4, vitamin E, mcnadoxime, menadiol, and vitamin K5-

Another embodiment of the invention is the compound of formula I, wherein D^1 and D^2 represent the same therapeutic agent to give a symmetrical double prodrug. Another embodiment of the invention is Une compound of formula I, wherein D^1 atwi D^* represent different therapeutic agents to give a rrottual prodrug. Another embodiment of the $i\beta vc$ (Iten is the compound of formula (I), wherein D^1 and D^2 can be cite—from same or different therapeutic class. Mothej ambodimeixt of the invention is the compound of formula (I)₄ wherein D^1 find D^2 can be same or different therapeutic agents, Srøfo therapeutic agents may have same or different mechanisms of action or fljey may work on different biological targets Q work on different disease conditions.

Another embodiment of the invention is the compound of formula I, whereia D^2 is R^2 , R^3 or R^4 . Another embodiment of the invention is the compound of formula I, wherein a is 0, B i\$ S-S, S»S=O, S-SOa or S-S=NH, Yet another embodiment of the invention js the compound of formula I, wherein a is 0, B is S-S or S-S=O, S-SOn $m\dot{\alpha}D$? is R^2 or R^3 or R^4 . A further embodiment of the invention is the compoind of formula J, wherein B is S-S_>A and A¹ are CH₂-CHz, E is a boad and D^2 is R^a , R^3 or R^4 .

Another embodime&t of the motion is\he compound of fo π nula I₁wherein a is 0; B is S-S or S-S-O, S-SO₂; A and A¹ are CH₂-CH₂, E is a bond and D* is R⁴. Mother embodiment of the invention, is the compound of formula I, wherein a is 0; B m S-S; A and A¹ are CHj-CH₂, E is a bond and x>z is R⁴.

Another embodiment of the invention is the compound of formula 1, wherein a is 0, B is a bond, (CHaX or (CHiCH $_2$ O) $_0$; wherein b and c are as defined above. Another embodiment of the invention is the compound of foimula I, wherein a is 0, B is a bond, (Cf \ddot{l} i)b or (CHJCHJO)C and D 2 is R 2 or R 3 or R 4 ; wherein b and c are as defined above.

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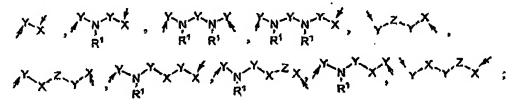
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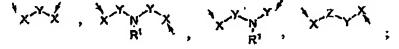
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Yet another embodiment of the invention ig the compound of formula I, wheiein a is 0; B is S-S or S-SO ₃ S-SO₂J D¹ attd D² are drug molecule of R? or R⁴ containing carboxyl group; L¹ and L^a are independently selected from the following linkages;



wherein, X, R^1 , Z are as defined above; and Y is C=O. The another embodiment, A and A^1 are CBfe-CKfe, and E is 4 hood, In a rurther embodiment, A and A^1 are $\frac{1}{2}$ -phenylenev U 3-phenylene or $\frac{1}{2}$, 4-phenylene, £md E is CHa.

Yet another embodinaeat of ftie invention is the compound of formula I, wherein a is O, B is S-S or S-S-O, S-SO₂; D^1 and D^2 are diag molecule or B? or R^4 containing amino- or hydroxy! group*, L^1 and I? at independently selected ftora the following linkages:



wherein, X, R^J, Z are as defined; and T is CK). In sobUier einboditnent, A attd A¹ are CHb-CH₂, and E is a lo&&. In a further embodiment, A and A¹ are 1, 2-pheaytene, 1, 3-phenyleti β or 1, 4-ph/ssfty)ieBe, and E is CHz.

Yet another embodiment of the invention is the compound of fotnnrta I, wherein a is O₁ B is S-S or S-SK)* S-SO $_{\Sigma}$ and D^a is D¹. Another embodiment of $\dot{\omega}$ e invention is the compound of foKraula I, wherein a is O; B is S-S or S-S^=O, S-SO₂; A and A¹ are M_{2} -

CH₂, E is a bond and D² is D¹. Another embodiment of the invention is the compound of fott Λ ula I_0 wherein a is 0; B is S-S or S-S=O, S-SO₂; A and A¹ are 1,2-phenylene, 1,3-phenylene or 1,4-phenylene; E is CH₂ and D² is P ¹O R² or R³ or R⁴. Another et Cbodkient of & β invention is the compound of formula I, wherefo a is O, B is S-Sj A and A¹ are I^-phenylene, 1,3-phenylene or {,4-pnenylene; E is CH₄ and P² is P ¹O R² or R³ or R⁴. A fittiffier embodiment of the invention is the compound of formula I, wherein B is S-S, A and A¹ are CHa-CH^ E is a bond and t)² is t>1

Yet another embodiment of Λ e invention is the compound of formula 1» wherein a is 0; B is S»S or S-S-50, S-SO₂; A and A¹ are CH₂-CIJb, E is a bond anfl f is a dipept ide ligand. Yet another embodiment of the invention is the compound of formula I. wheretøi a is 0; B is S-S; A and A¹ are CH2-CH₂, E is a bond and P² is adipeptide ligand. The peptide ligands used in the invention can be substrates for intestinal transporters for selective intestinal absorption of the corresponding prodrugs thereby increasing the bioavailability of the prodrugs. An embodiment of the present invention is the compounds of formula (t), wherein D¹, L¹ and L² are as defined above; A and A¹ are CHa; E is Cïé B is abond or (CH2)_b; b is 1-6; a is O; and D³ is D¹ or R² or R⁴.

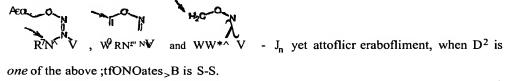
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Another embodiment of the present invention is the compound of formula (I)₅ wherein E, D*and V are as defined; L³ is O; A a Of A ¹We independently (CH2>, 1,2-phenyleae, i β -ph β ayleii $^{\wedge}$ or 1,4-pheftytett β , d is 1-4; B is S-S, S-S=O, S-SOa or S-S=TJH; a is O, D² i &NO, NO₂ of a ω tric oj ode releasing naoleotile sttch as KONOate. In a farther embodiment,!)? is a>IONOate selected from the groi Ψ consisting of:



Another embodiment of the present invention is the compound of formula (1), L^2 is O; A and A^1 aj_f β independently $(CH_2)_{dj}$ 1,2-phenyïenc, 1,3~p:henylene_> or 1,4-pheaylene; d is 1-4; B is S-S; a is O; $\mathcal F$ is NO₂. In a fbrfher embodiment, when A wid A^1 CH_2 - CH_2 , E is a bond, fa yet another embodimeM, when E is CH_1 , A and A^* ate independently 1.2-phfenylenc, 1,3-phenylene, ot 1,4-phenylene.

Yet another embodiment of the present invention is the compound of fonn.uk (I), whet Ein D! is an amino containing drug molecule having Hie following reactive functional groups which are involved in the formation of L¹ linkages between the drug and the linker. -NH₇, -NHR¹, -CQNHR¹_> *O-C(=O)NRR\ -SO₂NHR¹, -OSOiNHR¹, -NR¹CC=O)NHR¹ or -N(^)SO ₂NHR¹; L² is O; B is bond; L¹ is linkages selected from the group consisting of:

wherein, X is independently a bond, O or NR\ Y is O O or SO_2 , A and A^1 are CH_2 , B is S-S, a is Oand T? is NOj.

An embodiment of the present invention is the compound of formula (i), Wherein P¹ is a hydroxy! or sulfatoydtyt contaming drug molecule sufth as Drag-OH or Druig-SH, wherein ftmctional groups OH and SH are involved in the formation of L* linkages between the drug and the linker; L² is O; E is bond, L¹ is a linkage selected j&om the group consisting of:

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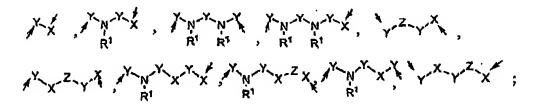
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wherdn, X is independently a bond, O or NR\ R*is not a bond, Y is O O or SCtø, A and A¹aie CH₂CH₂; B is S-S; a is O; and D² i? WO₂.

An embodiment of &e present invention js ihe compound of formula $(I)_3$ wherein D^1 is a drug molecule having carboxyl (- CO_2H) as a reactive ftn G ioiial group such as - CO_2H which is involved in the formation of L^1 linkages between the drug and the linker; M is O; M is M is M or M or M is M or M is M or M is M or M is M in M in M in M is M in M in M in M in M in M in M is M in M is M in M i



wherein, X is independently a bond, O ox NK.¹, R¹ is not a bond; Y is C=O or SO_2 ; A and A¹ are CH₂CH2; B is S-S; a is Oand D² is NOz.

Another embodiment of the present invention is the* compounds of formula (I), wherein D is m antioxidant or free radical scavenger sach as a hydroxyl-cont β iung stable radical suck a4^ydroxy-2 $_{7}$ 2,6,6-tetranae1hylpiperidin-l-oxyl (4-ftydroxy-TEMPO), 4-cart>oxy "2 Λ 6,6"tcteam^ylpiperidwirl-0Hyl (4-cacbo χ y-TEMPO) or any other jraM π o-Zcajboxyl./hydtoxyl-contai π ling antioxidants or radical/super oxide scavengers* and D² is NQ*. The amino-/c«t>oxyl-/hydroxyl-coRtaining antioxidants and radical/super oxide scavengers cant be knovrø, ot investigational.

An embodiment of the present invention is the compound of formula (I), wherein

$$L^1$$
 is X or R^1 ; wherein, X is a bond, O , S or NR^1 ; L^2 is O , E is a bond; A and A^1 are CH_2CH_2 ; E is S - S ; E is C ; and E is NO_2 .

An embodiment of the present invention is the compounds of formula ϕ , whetejn V^* and L^* are as defined above; L^* is O; A is 1,2-phenyl β ne, 1,3-jshenylene, or 1,4-phenylene; A^* is CH&E is CH« B is S-S; a is O and D^2 is NO_2 .

An embodiment of the present wiveroi on is the compounds of formula Q)» vrtietein I_2^{β} is O; A and A¹ are CHi E is CH₂; B is a bond or (CH₂)H; b is 1-6; a is O; D² i ${}^{\beta}$ NO₂ and L¹ is a group selected firon,

wherein, X is O, S or NR 1; R v is as defined.

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An embodiment of the invention is tfre compound of fomnrta I selected from the groups consisting of:

A. Prodrugs:

'n

(a) From carboxyl-containing drugs:

(b) From amino-containing drugs:

R_{y1} = An amino-, hydroxyl-containing molecule with water-solubilizing groups I-A2-PD5

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s=1,2; Ral = H, OH, NH2, or a substituted amino group I-A3-PD6

R²² = Me or any alkyl, aryl, aralkyl, or another sulfonamide containing drug such as valdecoxib, celecoxib, and the like.

I-A3-PD7b

(c) From hydroxyl-containing drugs:

I-HI-PD14

$$X^{1} = H, X^{2} = 0$$

$$X^{1} = H, X^{2} = 0$$

$$I-Taxol-PD1: R^{222} = H$$

$$I-Taxol-PD2: R^{222} = C(=0)CH_{2}CH_{2}CO_{2}H$$

$$CH_{3} = H, X^{2} = 0$$

$$I-Taxol-PD3$$

$$X^{1} = H, X^{2} = 0$$

$$I-Taxol-PD4$$

$$X^{2} = H, X^{1} = 0$$

$$X^{2} = H, X^{1} = 0$$

$$X^{2} = H, X^{2} = 0$$

$$X^{2} = H, X^{3} = 0$$

$$X^{3} = H, X^{3} = 0$$

$$X^{4} = H, X^{5} = 0$$

$$X^{5} = 0$$

$$X^{5} = 0$$

$$X^{7} =$$

A PRODRUG OF ISOTAXEL I-823-PD1

Y = O, NR^1 ($R^1 = H$, Alkyl, Aralkyl, Cycloalkyl), (CH_2)₀C(=O) (n=1-6), (CH_2)₀ CO_2^- Z = C=O, SO_2 , $P(=O)YR^3$ ($R^3 = H$ or a metal ion)

 $R^2 = H$, a bond, $CH_2CH_2N(CH_3)_2$. HCl, an Amino acid, or any molecule containing solubilizing groups such as carboxylic acid, sulphonic acid, hydroxyl, amino groups, polyethyleneglycol (PEG), a metal ion such a Na^+ , Ca^{2+} , etc.

B. NO-releasing Prodrugs

(a) From earboxyl-containing drugs

(b) From amino-containing drugs

(c) From hydroxyl-containing drugs

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C. Mutual or Double Prodrugs

(a) From two amino-containing drugs

 $R^{an1} = H$, PO_3H_2 , $C(O)NHCH_2CH_3NMe_2$, C(O)CH2NR'2 (R' = H or Alkyl), $C(O)OCH_2CH_3NMe_2$, $C(O)CH_2CH_2CO_2H$, $C(O)NHCH_2CH_2NHCOCH_2CH_3CO_2H$, $C(O)O(CH_2)_2NHCO(CH_2)_2CO_2H$, and $C(O)CH_2N(CH_2CO_2H)_2$.

LAA-MPD3a ($R^{an1} = H$)

(b) From two carboxyl-containing drugs

(c) From two hydroxyl-containing drugs

(d) From an amino-containing drug and a carboxyl-containing drug:

(e) Mutual prodrugs of one carboxyl-containing and one hydroxyl-containing drugs

(f) Mutual prodrugs of one amino-containing and one hydroxyl-containing drugs

Afl. embodiment of the $\dot{\eta}$ i^y ention is a pharmaceutical composition comprising a therapeutically effective amount of the compound of fitranulla I, or a pharmacfeutical salt thereof and one or more pharmaceutically acceptable earners, vehicles or diluents.

Another embodiment of the invention is a pharmaceutical composition 5 comprising a therapeutically effective amow Te of the compound of foxmula I selected from the group consisting of I-C1-PD1, 1-C1-PD2, I-C1-PD3, I-C1-PD4, Kl-RMa i-CI-PD4b, I-C1-PD5, I-C1-PD6, I-C1-PD7, I-C1-PD8, I-C1-PD9, I-Ct-PDIO, hCh PBI 1, J-C1-PD12, Ï-C1-KM, Ï-CI-PD14, 1-CI-PD15a, I-CI-PD15b, Ï-A1-PD1, I-Al-PD2, r-Al-PP3, 1-A1-PD4, 1-AI-PD5, 1-A1-PD6, 1-A3-PD7, M1-PD8, 1-A1-PD9, 1-A1-PDIO, I-A1-PD11, 1-Al-Hn2,I-Al-PD13, 10 Ï-A1-PD14, 1-A1-PD15A, I-AI-PDISAa, x AI-PDJSB, 1-AI-PDISBb, ÏA I-PD16, 1-AI-IPD1?, I-A2-PD1, J-A2-PD2, ^AZ^DZb, I-A2-PD3a, I-A2-PD3b, Ï-A2-PD4, 1-A2-PD5, 1-A3-PP1, 1-A3-3PD2a, Ï-A3-PD2b, I-A3-PD3a, I-A3-PD3b, I-A3-PD4, 1-A3-PD5, 1-A3-PD6, 1-AS-PD^ I-Hi-PDI, I-HI-PD2, 1-H1-PD3, 1- H1-PD4, "- H1-PD5, 1- H1-PD6, 1- H1-PD7, 1- H1-PD8, 1- H1-PD9, 1- H1-PDIO, I- HI-PDH, I- m-FDU, I- HI-PDI3 s 1-Taxol-PDÏ, I-Ta κοΙ-PD2, 1-Taxol-Pi>3, 15 I-Taxol-PD[^] I-Taxol-PD5,I-Taxol-PD6 ₂1~S23*PD1, X-CI-NOPDI, I-C1-NOPD2, T-Cl-NOFWa, I-CI-NOPD3b, J-C1-NOPD4, 1-CI-NOPDSa, I-CI-NOPDSb, 1-C1-NOPD6, J-C1-NOPD7, 1-Cl-NOPDSa, I-Cl-NOPDSb, I-CJ-NOPD9, 1-C3-NOPD10, 1-Cl^ sI-CI-NOPDH^I-CI-NOPDIAl sI-CI-NOPDISbJ-Cl-NOPDIm-CI-NOPPIS 20 NOPDilδ. I-CI-NOPDHa, Ï-CI-NOPD17b, I-C1-NOPD18, tCl-NOPDI?, Ï-Ct-NOPD20a ₂I-Cl-NOPD20b, I-Cl-KOPD21, Ï-Cl-NOPD22, 1-CÏ-NOPD23b, I-Cl-NOPD24, 1-C1-NOPD25, 1-C1-TS(OPOa 4 1-A1-NOPD1, $\ddot{1}$ -A1-NOPD2, 1-A1-NOPD3A, I-A1-NOPD3B, I-A1-NOPD4, 1-A1-NOPD5, 1-A1-NOPD6, 1-AI-NOPD7, 1-A1-NOPD8 "I-A1-NOPD9, 1-A1-NOPDIOa, J-A1-NOPDIOb, Jf-A2-NOPD3a, I-A2^ 25 NOPDIb, I-A2-NOPD5a, I-A2-NOPD2b, Ï-A3-NOPDIa, I-A3-NOPDIb, I-A3-N0PD2a, I-A3-NOPD2b, I-HI-NOPDI, I-HI-NO-?D2a,I-HI-NOPD21) 2I-H1-N0PD3, 1-1-Hl-NOpDIO 3 1-AA-MPD1, 1-AA-MPD2, ^AA-MPD3a, Ï-AA-MPD4, 1-AA-MPD5, 1-AA-MPD6, 1-AA-MPD7, 1-AA^MPP β, I-AA-MPD9, 1-AA-MPD10, Ϊ-AA-MPDU, Ι-AA-MPD12, 1-AA-WPD13, 1-AA-MPD14, 1-AA-MPDJ5, 1-AA-MPD16, 1-AA-MPD17, 30

I-AA-MPDI8, 1-AA-MPD19, 1-AA-MPD20, 1-AA-MPD21, 1-AA-MPD22. Ï-AA-

MPD23>I-AA-MPD24, I-AA-MPD25; I*AA-MPD265 I-AA-MPD27, WX-MPDI, I-CC-MPD2, 1-CC-MPD3, I-CC-MPD4, I-CC-MPD5, I-CC-MFD6, Ï-HH-MPD1, I-HH-MPD2, I-HH-MPD3, I-HH-MPD4, I-HH-MPD5, MIH-MPD6, I-HH-MPD7, I-HH-MPD8, 1-HH-MPD9, 1-HH-M.PDIO, I-HH»MPD11, Ï-HH-MPD12, 1-HH-MPD13, I-HH-MPDH , 1-HH-MPD15, 1-HH-MPD16, 1-HH-MPD17, 1-HH-MPD18* I-HHAH-TMPDJ, Î-CA-MPD1, 1-CA-MPD2, 1-CA-MPD3» I-CA-MPD4, 1-CA-MFD5, 1-CA-MPD6, 1-CA-MPD7 a I-CA-MPD8, 1-CA-MPD1 I-CA-MPD10, 1-CA-MPD11, 1-CA-MPD12, J-CA-MPD12, J-MPD13, Ï-CA-MPD14, Ï-CA-MPD15, I-CA-MPD16, 1-CA-MPD17, KA-MPD18, 1-CA-MPDJ 9, Ï-CA-MPD20, 1-CA-MPD21, 1-CA-MPD22, 1-CA-M?JD23, 1-CA-MPD24, I-CA-MPD25, 1-CA-MPD26, 1, CA"MPD27 SI-CA-MPD28, 1-CA-MPD29, 1-CA-10 MPD30, 1-AH-MPD1 , Ï-AH-MPD2, 1-AH-MPD3, 1-AH-MPD4, Ï-AH-MPD5, 1-AH-MPD6, 1-AH-MPD7, 1-AH-MPD8, 1-AH-MPD^ J-AH-MPDtO, I-AH-MPD11, 1-AH-MPD12- I-AH-MPD13, Ï-AH-MPD14, 1-AH-MPD15, 1-AH-MPD16, K-AH-MPD17, Ï-AH-MPD18, 1-AH-MPD19, 1-AH-MPD20, Ï-AH-MPD21, 1-AH-MPP22, 1-AH.MPD23, I-AH-MPD24, I-AH-MPP25, I-AH-MPD26, I-CH-MP]DI₁Ï-CH-MPD2, I-CH-MPD3, I-CH-MPD4,, I-CH-MPDS, and I-CH-MPD6 or a pharmaceutical salt thereof and on@or mote pharmaceutically acceptable earners, vehicles or diluents.

An embodiment of the invention is a method of treating a mmaml or human in tteed thereof comprising administering a therapeutically effective amount of the pharmaceutical composition $coj \Phi$ cisrag the compound of foirøvila I

Another embodiment of the invention is the below listed novel intermediates:

2-((2-Hydroxyethyl)disulfanyl)ethyl acetate (LI-1a)

2-((2-(Trityloxy)ethyl)disulfanyl)ethanol (**LI-1c**)

2-((2-Hydroxyethyl)disulfanyl)ethyl nitrate (LI-2b)

2-((2-Hydroxyethyl)disulfanyl)ethyl nitrate (LI-2c.TFA)

tort-Butyl 2-((2-bromoethyl)-disulfanyl)ethylcarbamate (LI-2e)

1,2-Bis(2-bromoethyl)disulfane (LJ-3a)

2-((2-Aminoethyl)disulfanyl)ethyl nitrate.acid salt (LJ-5.TFA)

2-((2-(Tetrahydro-2H-pyran-2-yloxy)ethyl)disulfanyl)ethanol (LI-1b)

2-((2-Hydroxyethyl)disulfanyl)ethyl 2-chloxoacetate (LI-1d)

2-((2-Bromoethyl)disulfanyl)ethanol (LI-2a)

tert-Butyl 2-((2-hydroxyethyl)disulfanyl)ethylcarbamate (LE-2c)

2-((2-(tert-Butoxycarbonylamino)sthyl)disulfanyl)ethyl methanesulfonate (L1-20)

tert-Butyl 2-((2-(nitrooxy)ethyl)-disulfanyl)athylcarbamate (LI-21)

2,2'-Disulfanediyibis(ethane-2,1-diyi) dinitrate (L1-3b)

2-((2-Aminoethyl)disulfanyl)ethyl nitrate (LA-5)

2-((2-Bromosthyl)disulfanyl)ethyl carbonochloridate (LI-6)

Aflother embodime»t of the invention is use of flic above listed novel mtemiediates in the processes for the preparation of compounds of formula I.

disulfarryl)ethyl 2-(dimethylamino)ethylcarbamate (LI-10)

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Further embodiments include method3 of preparation and methods of use of compounds of førømla (I) or phama awticaUy acceptable salts thereof.

Another embodiment of the invention is process for the preparatiüïi of compounds of formula I, or pltaπoaceuticalïy acceptable salts thereof wherein the process comprises of:

moβoprotection of Bis-(2-hydroxyethyl)disulphide (SL-I) with 3» appropriate hydroxyl protecting group to give a corresponding monoprotected intermediate,

convcarsion of the corresponding monoprotected intermediate b aa activated foroiyl intermediate by treating with phosgene or its equivalent* and

reaction of the activated formyl intermediate with an appropriate amino- or hydroxy containing D^1 to give the corresp and βg compound of formula I.

Another embodiment of the invention is a process for the preparation of compounds of formula I, or pharmaceutically acceptable satøs thereof, wherein the process comprises of:

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-converting catboxy containing P I into an activated intermediate comprising acyl halide, imidazoline or jsocyanate, and

-reacting the activated intermediate with a linker intermediate to obtain the compound of formula I.

In anotiier embodiment, the invention is a process in which the monoprotected interediate is LIIx, and the activated formyl intermediate is LIIxy,

Another embodiment of the invention is a, process fo* preparation of compounds of forrøutø. <t), wherein D* is NOj or pharmaceutically acceptable salts thereof, wherein the pwc βss comprises, mixing a selectively protected and activated DI with a solution of 2'((2-JjydroxyethyJI)dithio)e(hyl nitrate 0LK2b) in a suitable solvent in presence of a suitable coupling agent

Another embodiment of the invention is a process for preparation of compounds of formula (I), wherein if is NO2 or pha π nacetitically acceptable salts thereof, wherem a process comprises, converting 2-(C2-h.ydtoxyetnyl)dithio)ethyl nttrate (LI-2b) into its formyl hajide or i» Údazolide (LI-4x) by using a phosgene or its equivalent reagent and mmtogfreaeting the resulting reactive intermediate with a suitable amino- or hydrøxy-co&taming drug in suitable solvent in presence of a suitable base.

Another embodiment of the invention is a process for preparation of compounds of formula (T), -wherein D² is NO[^] or pharmaceutically acceptable salt thereof, whereim the process comprises, joixing/reacting a selectively protected and activated drug with a solution of 2-((2-atoiDoetJxyl)ditbio)c%l nitrate (LI-5) in a suitable solvent in presence of a suitable coupling agent and/ot base.

Another embodiment of the invention is a process for preparation of mutual prodrugs of compounds of formula (I), or pharmaceutically acceptable salts thereof, wherein a procegs comprises,

A) iponoprotection of Bis-(2-hydfoxyethyl)disu]pHde (SL-I) with an appropriate hydrøxyl protecting group to give the corresponding monoprotected intermediate LHx, B) reaction of formylli π ker mtermediate LI-lxy with amino or hydroxyl containing drug (D') to obtain, the prodrug of formula I with free hydroxyl group on the linker, C) conversion of the intermediate obtained in the step B into activated formyl halide or *imidazoline* derivative, and

10 D) reaction of the intermediate obtained In the step C with flie drug D* to obtain the mutual prodrug of formula I.

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Further embodiments of the ittveOtion are processes for the preparation of compounds of $\mathbf{\hat{s}}$ π nula I, or pharmaceutically acceptable salts Uiereof, wherein the processes comprise of the steps that are generally depicted in the schemes 1-23.

Further embodiments include the pharmaceutical composition comprising a therapeutically effective amount of novel intermediates or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers, -vehicles or diluents.

A β oHier embodiment of the inveotion is use of compounds of formula Q or pharmaceutically acceptable salt thereof, In the treatment of disease conditions originally treatable by the corresponding free drug(s)»

It should be understood that while this Invention has been described herea itx terms of specific emboclij»eix-s set forth in detail, such embodiments are presented by way of illustration of the general principles of the invention, and the invention is not necessarily lire ited thereto. Certain modifications and variations itt any given raafteri-tf, process step or chejmical formula will be readily apparent to those skilled in the art twithout departing from the true spirit and scope of the present invention, and all such modifications and variations Should be considered within, the scope of the claims that follow. The cootents of the articles, patents., and patent applications, and all other documents mentioned or cited herein, are hereby incorporated by reference in their entirety to the same extent as if each individual publication was specifically $m \dot{\alpha}$ individually indicated to be incorporated by reference.

Yet another embodiment of the invention is a compound of formula I containiting ait amino-contaii in the group of the invention is a compound of formula I containiting ait amino-contaii in the group of the group o

Another embodiment of tile invention is double prodrug of $fo\pi\pi$ ula (I) selected fym the group consisting of: I-AA-MPD5, Ï-AA-MPD6, Ï-AA-MPD7, and I-AA-MPD8.

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The present invention also provides mutual prodrugs of formula (I) selected ftojn tba grøup consisiting of: I-CA-MPD1, I-CA-MPD2, 1-CA-MPD3, r-CA-MPP4, I-CA-WDS, I-CA-MPD6, I-CA-MPD7, I-CA-MPD8, I-CA-MPD9, T-CA-MPD10, I-CA-MPD11, I-CA-MPD12, Ï-CA-MPD13, I-CA-MPPH, I-CA-MPD15, I-CA-MPD16, I-CA-MPD17, I-CA-MPD18, 1-CA-MPD19, 1-CA-MPD20, 1-CA-MPD21, I-CA-MPD22, I-CA-MPD23, I-CA-MPD24, I-CA-MPD25, Ï-CA-MPD26, I-CA-MPD27, I-CA-MPD28, 1-CA-MPD29, mαI-CA-MPD30.

In another embodiment, the invention provides compounds of formuja (J) selected from tile giwup of mutual prodrugs made from ammo-containing therapeutic agent and a hydroxyl-coOtaining therapeutic agent such as: I-AH-MPDI, I-AH-MPD2 > I-AH-MPD3, I-AH-MPD4, I-AH-MPD5, I-AH-MPD6, I-AH-MPD7. I-AH-MPD8, I-AH-MPD9, ï« AH-MPD10, I-AH-MPDU, I-AH-MPD12, Ï-AH-MPD13, I-AH-MPD14, 1-AH-MPD15, I-AH-MPD16,)t-AH-MPD17, I-AH-MPD18, I-AH-MPD19, I-AH-MPD20, I-AH-MPD21, I-AH-MPD23, 1-AH-MPD24, 1-AH-MPD25, audI-AH-MM>26.

Yfit another embodiment of the invention* relates to compounds of formula ϕ of mutual prodrugs made from a hydroxyl-contaming therapeutic agent and a hydroxyl-containing therapeutic agent such as; I-RH-MPD1, 1-HH-MPD2, 1-HH-MPD3, I-HH-MPD4, I-HH-MPD5, Ï-HH-MPD6, I-HH-MPD7, I-HH-MPD8, I-HH-MPD9, tHH-MPD10, Ï-HH-MPD11, Ï-HH-MPD12, Ï-HH-MPD13, 1-HH-MPD14, 1-IÏH-MPD15, 1-HH-MPD16, K-HH-MPD17, and I-HH-MPD18.

The present invention also provides compounds of foπnula (I) containing water-soluble prodrugs of insoluble or spariagly-soluble therapeutic agents such as: 1-HI-PDI, I-HI-PD2, 1-HI-PD3, I-HI-PD4, I-HI-PD5, I-HI-PD6, I-HI-PD7, I-HI-PD6, I-HI-PD9, I-HI-PD10, I-HI-PD10, I-HI-PD12, I-HI-PD13, I-AI-PD2, I-AI-PD3, I-AI-PD4, I-AI-PD5, I-AI-PD6, MI-PD7, I-AI-PD8, I-AI-PD9, I-AI-FD10, I-AI-PD11, I-AI-PD12, I-AI-PD13. I-AI-PDH, MI-PD15A 5 I-AI-PD1Aa, I-AI-PD15B, I-A

PDISBb, I-ΛX-PD16, I-AI-PDH, S-A2-PD1, I-A2-TO, I-A2-PD2b, I-A2-H>3a, Ï-A2-PD3b, 1-A2-PD4, I-A2-PD5, I-A3-PD1, I-A3-H>2a, I-A3-Pmb, I-A3-PD3a, I-A3-PD3b, 1-A3-PB4, I-A3-PD5, 1-A3-PD6, I-A3-PD7b, I-HI-FDI* Ï-H1-PD2, 1- HM»D3, 1- HI-PD4, 1- H1-PD5, t- H1-PD6, 1- H1-TO, 1- H1-P08, 1- H1-PD9, I* HI-PDIO, t- Hi-PDII, I- H1-ID12, 1- H1-PD13, t-Taxol-PDt, I-Taxol-PD3, 1-Taxol-PD4 5 Ï-Taxol-PD5, PTaxol»PD6, βή«II-S23-PDI,

Another embodiment of *he iaveation relates to the compounds of fojcmula (T), selected from U\e group of NO-f \(\beta \) leasing p\(\beta \) onsisting of: 1-Cl-NOPDI 2 l-Cl-N0PD2 "I-Ci«.NOPP3a, I»CI-NOPD3b, Ï-CI»NOPP4, I-CJI-N0]?D5a, I-Cl-N0PD5b, Ï-C1-NOPP6, Ï-C1-NOPD7, U-C1-NO)PDSa₅1-Cl-NOPD8b, I-C1-NOPD9, 1-Cl-NOPD10, J-Cl-NOPDJIa, I-Cl-NOPD13, 1-c µNOPD14a, I-Cl-NOPDMb 51-Cl-NOHUSb, I-Cï-NOPM7a, I-CI-NOPD17b , I-C1-NOPD18, I-C1-N0PD19, X-CI-NOPD20a, I-C μ NOPD20b, X-C1-N0PD2 Ï, Ï-C1-N0PD22, J-CI-NOPD23b, I^CI-NOPD24, Ï-C1-NOPD2S. I-CI-NOPD26, 1-A1-NOPD1, Ï-A1-NOPD2, Ï-A1-NOPD3A, Ï-AI-NOPD7, *l***M*− I-A1-NOPD3B, I-A1-NOPD4, tAl-NOPDS, 1-A1-N0PD6, I-Al-NOPDIOb, 1-^ I-A2-N0PDK NOPD8, I-A1-NOPD9, I-Al-HOPDIOa, I-A3-NOPD Tb, I-A3-NOPDIb, ï»A2-N01?D2a, I-A2-NOFD2b, I-A3-NOPDla, N0PD2a, "-A3 «NOPD2b, I-H1-NOPD1, 1-H1-NOPD29, I>BI«N0PD2b, I-H1-NOPD3, I-H1-N0PD4, 1-HI-N0PDSb, I-H1-N0PD6, 1-H1-N0PD7, Ï-H1-N0PDS, I-HI-N0PD9, \ddot{i} -HI-NOPm θ .

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. Another aspect of the invention provides tixe tise of the compounds of formula (I) in combination with a cojmpound used to treat cardiovascular diseases selected from the group consisting of: beta adrenergic blockers, calcium channel blockers, angiotensin H receptor antagonists, antithrombotics, HMOCoA reductase inhibitors—aspirin or Ottrooxy derivatives of aspirify flittosated beta blockers, jatrosated or nitrosilated calciura channel blockers. Suitable drugs are described in the lit βrøt Otte such as the Merck index, ID«». Prous Sciences integrity*, Prøus Science Owgs of the FutureTM, The Efiaemblβ®an<s the like.

Mother aspect of the inveotem provides the use of the pharmaceutical compositions containing compounds of formula *Q* in combiMation with a compound, «std to treat other diseases such as cardiovascular diseases, selected from beta adrenergic blockers, calcium chanael blockers, angiotensin U receptor antagonists, antithrombotics,

BMGCoA reductase inhibitors, aspirin or nittooxy derivatives of aspirin, nitrosated beta blockers, nitrosated or nitrosilated calcium channel blockers. Pharmaceutical compositions containing two or more of compounds of the invention can be used for the purpose of combination therapy. Tliese pairs of compounds of invention; can be from the same therapeutic area or from different therapeutic areas for treating one or more diseases or conditions.

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Ifte compounds of the invention, which have one *or* more asyxnnaetric carbon atoms, can exist as the optically pure enantiomers, pure diastereonicrs, enantiorner racemic mixtures, diastereoraer racemic mixtures, racemates or racemate mixtures, Within the scope of the invention are also all the possible isomers, stereoisomers and their mixtures of the compounds of formula (T).

Another embodiment of the invention relates to the pharmaceutical composition comprising one or more compounds of formula Ct) or pharmaceutically acceptable salts thereof and one or more pharmaceutically acceptable earners, vehicles or diluents.

Another embodiment of the invention relates to the pharmaceutical composition comprising one or mote compounds of formula ϕ or pharmaceutically acceptable salts thereof and at least another pharmaceutically active compound. The pharmaceutically active compound can be from the same or different therapeutic areas for treating one or more disease conditions) together with one or more ptø π paceutically acceptable carriers, vehicles or diluents.

Further embodiments include methods of use of compounds of formula (!) or pharmaceutically acceptable salts thereof.

Another embodiment of the invention is a process for preparation of compounds of formula Q or pharmaceutically acceptable salts thereof, wherein the process comprises, mixing a selectively protected and activated ding with a solution of 2-((2-hydroxyethyl)dithio)etijyl nitrate in a suitable solvent in presence of a suitable coupling agent Another embodiment of the invention is a compound or intermediate generated in the above methods and processes.

Another embodiment of the invention is a process for preparation of compounds of formula (J) or pharmaceutically acceptable salts thereof, wherein a process comprises, converting 2-((2-hydroxyefiiyl)dithio)ethyl nitrate into its formyl halidβor imidazolide by

using a phosgene or its equivalent feagent and mixing/xeacti $\hat{\beta}g$ the resulting reactive intermediate with a suitable drag in suitable solvent in presence of a suitable base.

Another embodiment of the invention is a process for preparation of compounds of formula (I) or pharmaceutically acceptable salt thereof, wherein the process comprises, mixing/reacting a selectively protected, and activated drug witiE λ a solution of 2-((2-ami π oethyl)ditbio)6tiiyl nitrate (or its acid salt) in a suitable solvent in presence of a suitable coupling agent and/or base.

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Another embodiment of the invention comprises the novel intermediates formed in the preparation of present invention, Fwther etribOdiwients indude a pharmaceutical composition comprising a therapeutically eSective amount of novel intermediates or a phaitnaceutilcaMy acceptable salt thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.

Another embodiment of the invention is processes for the preparation of compounds of formula (I) or pha π naceutically acceptable salt thereof, as well as the starring materials and intermediates involved as depicted if schemes 1-23.

Another embodiment of the invention comprises the novel intermediates obtained in *Ike* preparation of comp Ut Ods of formula I, whereto the mtmnediates ate selected from:

2-((2-Hydroxyethyl)disulfanyl)ethyl acetate (LI-1a)

2-((2-(Trityloxy)ethyl)disulfanyl)ethanol (Li-le)

2-((2-Hydroxyethyi)disulfanyl)-ethyl nitrate (LI-2b)

2-((2-Hydroxyethyl)disulfanyl)ethyl nitrate (LI-2c.TFA)

terr-Butyl 2-((2-bromoethyl)-disulfanyl)ethylcarbamate (LJ-2e)

1,2-Bis(2-bromoethyl)disulfane (LJ-Ja)

2-((2-Aminocthyl)disulfanyl)ethyl nitrate.acid salt (LI-5.TFA)

2-((2-(Tetrahydro-2H-pyran-2yloxy)ethyl)disu(fanyl)ethanol (LI-1b)

2-((2-Hydroxycthyl)disulfanyl)ethyl 2-chloroacetate (LI-1d)

2-((2-Bromoethyl)disulfanyl)ethanol (LI-2a)

tert-Butyl 2-((2-hydroxyethyl)disulfanyl)ethylcarbamate (LI-2c)

2-((2-(tert-Butoxycarbonylamino)ethyl)-disulfanyl)ethyl methancsulfonate (LI-2d)

tert-Butyl 2-((2-(nitrooxy)cthyl)-disulfanyl)ethylcarbamate (LI-2f)

2,2'-Disulfanediyibis(ethane-2,1-diyl) dinitrate (LI-3b)

2-((2-Aminoethyl)disulfanyl)ethyl nitrate (LI-5)

2-((2-Bromoethyl)disulfanyl)ethyl carbonochloridate (LI-6)

Another embodiment of the iftventicm i_s tisc of compounds of formula (I) ox pharmaceutically acceptable salts thereox in the treatment of disease conditions originally treatable by the corresponding free drugs.

Another embodiment of the invention includes but not limited to a pharmaceutical composition comprising the compounds of formula (I), or plianoaceutically acceptable salt thereof, selected from the group of NO-releasing prodrugs described herein, or more pharmaceutically acceptable earners, vehicles or diluents.

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It should be understood that while this invention has been described herein in terms of specific embodiments set forth in detail, such embodiments are presented by—way of illustratio π of the general principles of th<≥ invention, and the invention is not necessarily limited thereto. Certain modifications and variations in any given material,

process step or chemical formula will be readily apparent to those skilled in the art without departing from the true spirit and scope of the present invention, and all such modifications and variations should be considered within the scope of the claims that follow. Hie contents of the articles, patents, and patent applications, and all other documents mentioned or cited herein, are hereby incorporated by reference by their entirety to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

POTENTIAL EXAMPLES OF MUTUAL PRODRUSS/CODRUGS:

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Mutual prodrugs made from an ammo-containing therapeutic agent and another amino-containing therapeutic agent;

A Mutual Prodrug of deslotatadke and pseudoephedrine (IA A-MPD1) is proposed as a potential treatment option for seasonal allergic rhinitis (SAR), Desloxatadine (an active metabolite of loratadine) is a new, non-sedating, locg-actiog histamine antagonist and has been shown effective. In the treatment of aasal and $\pi \circ \pi$ -nasal symptoms associated with SAR. Fssndoephedtfne is an oral decongestant

A Mutual Prodrug of amlodipine (Pfføcr's Norvasc ¹⁵¹) and lisinopril (Zeneca's Zestrfl®) (I-AA-MPD2) is proposed, as a potential treatment option for hypertension and congestive heart jfatlura. Amlodipine is a calcium channel blocker and is used as an antihypertensive and antianginal agent Lisiπopril is an -uigiotensin^converting enzyme (ACB) inhibitor and is used for fee treatment of hypertension and congestive heart failure. A combination therapy using these two drugs has been proven to be more effective treatment option fhan monotherapy using either of these <frug&

A Mutual Prodrug of amlodipine (Pftzcr's Norvasc*) and tosartan (Merck's Coaaar®) (I-AA-MPD3a) is proposed as a potential treatment option for mild to moderate hypertension. Affdodipine is a calcium channel blocker and Is used as an antihypertensive and antianginal agent Losartan potassium is an angiotensin II blocker and is used for the treatment of hypertension. A combination ttierapy using these two drugs has been proven to be more effective treatment option than monotherapy using either of &ese drugs.

Examples of mutual prodrugs and double prodrugs of valdccoxib and celecoxib containing a disulfide linker are: I-AA-MPD4 and I-AA-MPD5.

Examples of double prodrugs of vald&coxib or celecoxib containing noAdisuIfide linkers: I-AA-MPD6, I~AA-MH)7, I-AA-MH >8.

A Mutual Prodrug of fluoxetine (Lilly's Prozac®) and olanzapine (Lilly's Zyprexa®) *Q-AA-MPD9*) is proposed for potential treatment of patients with Bipolar disorder. Fluoxetine and Olanzapine are used ifl combination to treat patients with bipolar disorder while being spared the treatment-emergent mania that such patients of en get on antidepressant monotherapy.

Example of double prodrug of gabapqntin is proposed as potential antiepileptic agent: I-AA-MPD10.

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Mutual prodrugs made from an ami π D-containing therapeutic agent and a μ srb oi yl-contai π i π g therflpe otic agent:

A mutual prodrug of cetiri $2m\beta$ and pseudoepliedrine (I-CA-MPD1) is proposed for treatment of rhinitis Cettrizine is an antihistatnine and pseudoephedttte ia a tiasal decongestant.

Mutual prodrugs of gabapentin and valproic acid &w potestial antiepileptic agents. THs same kind of prodrug may be a potential treatment option for patients with bipolar disorder m i other mental illnesses. The fallowing are some of the examples:

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Other illustrative examples of mutual prodrugs under this category include the following: Mutual prodrugs of valproic add and other carboxyl-, hydroxy]-, and araiiio-contøinmg (including amide-, and sulføaaimde'c Ontaitiiftg) anticonvulsant agents such as Jevetiracetam, lamotrigine, pjcegabalin, carbamazepine,, oxcarbaajazepine, licarbazepme, felbamat^β, fopiramate and tlie like. (Structures are given below). Tfce list also includes investigational antiepileptic agents such as antipam βzole, licarbaz βpine, Eslicatbaaepine Acetate (BM. 2-093% fluorofeJbarøatβ, isovalerarøjde (NPS 3776), jetig βbiae p-23129), safbai ώde (NW-1015), sώipentol (STP), talampanel (TLP), (2S)-2-[(4R)^2-θκο-4-propylpy»oHdiii~l-yl]butananiide 83alpha (ucb 34714), valrocemid β (JV 1901), and the like.

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Mutual Prodrugs can >e made from combination of any two anti-co α mlsant ageats listed above or any other suitable aoticoavulsaat age $j\alpha p$.

Mutual prodrug of gabapeatim and jiapïoxett (J-CA-MPD22) is ptoposed for potential treaftneot option for neurological ps. n and inflammation.

Mutual prodrugs made from an amino-contaitting therapeutic agent and a hydroxyl-coiitaiiLing therapeutic agent:

Mutual prodrugs of norfloxacin and metronidazole (1-AH-MPDl₅1-AH-MPD2, 1-AH-MPD3) are proposed for potential treatment of diarrhea and dysenteiy of bacterial, amoebic and mixed ortg $\dot{\eta}\lambda$ Metronidazole is an antianaerøbic agent and used in combination with antibiotics such us norfloxacin, ciprofloxacin, etc. for the treatment of patients $v\dot{\eta}_{tix}$ diarrhea and dyseat&y of bacterial, amoebic and mixed origin.

A mutual prødtug of loperamide and norflaxacin (I-AH-MPD4) is proposed for potential treatment of diarrhea and dysentery.

A mutual prodrug of valdecoxib and tramadol (I-AH-MPD5 and tAH-MP $\ddot{l}>6$) as a potential tilerapy ia postoperative pain management

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A mutual prodrug of gabapentin and tramadol (T-AH-MPD7) is proposed for potential treatment of newopatbic pain after spinal cotd injuiy.

A mutual prodrug of venlafaxine and paroxetine (Ï-AH-MPDS) is proposed for potential treatment of neurological and depression related disorders.

Mutual prodrugs made from a hydro^containing therapeutic agent and another bydroxyl-containing therapeutic agents

Mutual prodrugs of zidovudine (AZrr/Retrovit) and $iai\pi ivudin\beta$ (3TC/Epmr) (I-HH-MPP1, I-HH-MPD2) are proposed as a potential treatm β tt option for HIV and other viral infections.

FOTEMIAL EXAMPLES OP WATER-SUIIBLE PRODRUGS:

Water-soluble prodrugs of iosoluble/sparingly'SoliJible thetapeuti δ agents can be prepared using the same linker technology.

Water-soluble prodrugs of metronidazole include: I-H1-PD-2, 1-H1-PP-3, 1-H1-PD-4.

W^ter-soluble prodrugs of valdecoxilb include: Ï-A3-PD1, Ï-A3-PD2a, I-A3-PD2b, I-A3-PD3a, I-A3-PD3b, tA3-PD4, 1-A3-PD5, 1-A3-PD6, nnd J.A3-PD7b.

Water-soluWeprodrugs of paclitaxel kehxte MwoWPDl, I-Taxol-PD2, 1-Taxol-30 PD[^]3 1-Taxol-PD4, Ï-Taxol-PD5, 1-TaxoRDo ", and I-S23-PDI.

POTENTIAL EXAMPLES OF NO-RELEASING PRODRUGS:

In the following potential examples, X is O, NR¹ (R¹= H, alkyl) or a bond; Y is CO, SO₂, P(=0)XR¹ or bond; R¹ is H, alkyl, aralkyl, or a metal ion; A is a bond, 1,4-/1,3-/1,2-phenylene or (CH2), (o = 0-6) and m is 1-2 unless otherwise stated;

Prodrugs of Valproic Acid (Anticonvulsant):

DRUGS CONTAINING REACTIVE FRIMARY AND SECONDARY AMINES, AMIDE-NEI, UREA-NEI, SULFONAMIDE-NEI, SULFAMATE-NH, AND CARBAMATE-NE:

Prodrugs of Gabapentin (Anticonvulsant):

(Anticonvulsant):

Prodrugs of Carbamazepine (Anticonvulsant):

NO-Releasing Prodrugs of Paracetamol/Acetaminophen (Analgesic and Antipyretic):

ADDITIONAL POTENTIAL EXAMPLES:

In the following additional potential examples, X is O, NR¹ (R¹= H, alkyl) or a bond; Y is CO, SO₂, P(=0)XR¹ or bond; R¹ is H, alkyl, aralkyl, or a metal ion; A is a bond, 1,4-/1,3-/1,2-phenylene or (CH₂)₀ (0 = 0-6) and m is 1-2 unless otherwise stated;

NO-Releasing Prodrugs of Nicotinamide:

NO-Releasing Prodrags of NSAIDs:

NO-Releasing Prodrugs of Aspirin

NO-Releasing Prodrugs of Paracetamol

NO Releasing Prodruga of Masolamine

NO-Releasing Prodrugs of Naproxen

NO-Releasing Prodrugs of Flurbiprofen

NO-Releasing Prodrugs of Ketoprofen

NO-Releasing Products of Indomethacin

NO-Releasing Produces of Improfene

NO-Releasing Prodrugs of Ketorolac

NO-Releasing Produces of Diclofenac

NO-Reicasing Prodrugs of Gincocorticoids:

NO-Releasing Produce of Prednisolone

NO-Releasing Prodrug of Ursodeoxycholic Acid

NO-Releasing Prodrug of Hydrocortisons

NO-Releasing Prodrug of Budesonide

:

NO-Releasing Prodrugs of Antioxidants and for Free Radical Scavengers:

NO-Releasing Product of TEMPOL (4-hydroxy-TEMPO):

NO-Releasing Prodrugs of Probucol and AGI-1067;

NO-Releasing Prodrugs of Lippic Acid:

NO-Releasing Prodrugs of Vitamin E (alfa-tucopherol):

NO-Releasing Prodrugs of Edgravone [3-methyl-1-phenyl-2-pyrazolin-Sone):

NO-Releasing Prodrugs of Antibiotics:

NO-Releasing Prodrugs of Metronidazole

NO-Releasing Prodrugs of Norfloxacin;

NO-Releasing Prodrags of Antiepileptic Agents:

NO-Releasing Produces of Valurolo Acid

NO-Releasing Prodrug of Gabapentin

NO-Releasing Prodrug of Levotiracetam

NO-Releasing Prodrug of Lamonigine

NO-Releasing Prodrug of Carbamazepine

gtøMb & Mechanisms of Drue Release f Utn Prodniea

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Drugs can be released from the prodrugs and mutual prodrugs via cleavage of biolabile linker(s) in vivo (cleavage can be either chemical or enzymatic or both) by illustøriive mechanisms as shown in Schemes M1 through M5.

Plausible mechanisms for concomitant release of nitric oxide (NO) and ftcc drug from NO-teleasiag prodrug® of amino-, hydrojsyl-, or carbojCy^conta Uijjtg drog(s) are illustratively shown in Scheme MI. Thus, the attack of thiokte ion (ftoft* GSH or any other sulfaJiydryl-contairang species) on lutrøoxy-comaining prodrug would release carboxylic acid-containing free drug, episulFide (d) and the intermediate conjugate (a) according to path 1-If the prodrugs are made from amino-, Oi hydroxyll-contakiing drugs, then the prodrug would be cleaved via path 2 to release the cpnespondittg fiee drug, the cyclic tbiocfljbotiate intendedtøte (c) and the intermediate conjugate (a). The cyclic thiocarbonate Intermediate may further breakdovm into episul $\beta d\beta$ (d) and, carbon dioxide. The tractive episul βde (fl) would be further neutralized by glutathione. The nitrate estercontaining intendediate conjugate can further break down in the presence of GSH to glutathione dimer (GS-SCS) and transient intermediate ϕ which can break down via path 3 to release NO. f is also possible that the same transient intemjediate can break down via path 4 to yield episutfide (d) and a relatively innocuous nitrate anion (NO₃).

X = 0, NR^1 ($R^1 = H$ or alkyl or a group linked to the drug) or a bond

Scheme M1

Plausible mechanisms of drug release from mutual prodrugs of one carboxyl-containing and one β m.no-%droxyl-conteicrøg djug is shown in Scheme JMZ

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Plausible mechanism of drug release *from* prodrugs (including mutual and NO-releasa Ttg prodrugs of amino-, hydrøxyl-and carbojcyl-containiftg drugs) containing modified bio-labiJe linkers is shown in Scheme M3. Thus, the tiiiolate aiuoa derived from the attack of glutathione on disulfide of the prodrug may trigger cyclizati Ct to please the free drwg (Dl-X h) and a stable six*nnembejred (ox fivfe-mejribered, if X?" is a bond) lhio4act<me interme Ctate.

 D^1 , D^2 and L^2 are as defined in the text. $X^{m1} = 0$, NR1 ($R^1 = a$ bond, H, alkyl, or a metal ion), CONR¹, SO_2NR^1 , P(O)NR¹, OC(O)NR¹, OSO₂NR¹ and the like. X^{m2} is a bond, CH₂, O, NR^{m1}(R^{m1} is H, alkyl, aryl or a bond), S, SO, SO₂ and the like

Releases the second drug or NO or promoiety via plausible mechanisms as shown in Schemes M1 and M2 Scheme M3

Plausible mechanisms of $\dot{\alpha}$ ug release from, doubles/mutual prodrugs containing additional linkages to couple two hydroxyl-contaming drags are shown in Stiheme M4. Thus, the thiolate anion gc $\pi\alpha$ ated $\ddot{i}\gamma$ the attack of glutathione on disulfide bond of the prodrug triggers fur&er cleavage as shown to jelcas β the free drug (p'-OH) and a JSvemenObered 2-i π ttda20lidonfe. Threnigh in vitro decomposition studies, we have found that the drug ielease from this type of pfodmg is more facile when R group is an alkyl group,

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This invention also covers novel faio-labil β linkers containing 2,4-ph β ayle π e group and I_j 2-phenylene gtoi ϕ as shown in Schemes S and δ_t irespectively. As depicted in Scheme M5, the linker is expected to release the free Drug 1 upon glutathione-assisted cleavage and may generate 1,4-qtrinonemetlijid (ea) as a byproduct via 1,6-climirøjtjon process. Similarly, the free Drug² is expected to be released from the intermediate conjugate (a) as shovrø iiti^je scheme.

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Scheme M5

As depicted in Scheme M#, the 1,2-phenylene-containing linker is also expected to release free drugs upon glutathione assisted cleavage and generate 1,2»quinonemethid (eb) as a byproduct -via 1,4-elimraatioi\(\mathref{O}\)process (via pathway V). However, this linker can also cleave via pathway 'a' b generate be\(\pi\)zo-monothiocarbonate as a byproduct Although the generated byproducts seem to be toxic, they are likely b be quickly neutralized by detoxification enzymes in the body.

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Scheme M7: Plausible mechanism of diezepem formation from an acyclic prodrug of diezepem

Water-soluble acyclic prodrug design for Diezepam

Diazepam, a b & Tzodiaze ρ (ie tranquilizer, is veiy sparingly wat β would water-soluble acyclic prodrug of diazepam can be made by W ing our linker tecktojøgy. As shown in the Scheme M7, reduction of disulfide bond a the prodrug triggers release of open-chain manufactured at the prodrug triggers at th

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Where GSH is glutathione (xedOced) or any other in vivo biotedu Give agext that can reduce the disulfide *hood*. As illustrated, cleavage of disulfide bond triggers further breakage of the fcrna $\dot{u}\dot{u}$ ng portion of fhe linker \dot{v} release the free drugs. If the process, some byproducts are generated and these are either eliminated or fttrther degraded by some biological process. For clarity, the mecfeanism of cleavage of the linket is shown as occurring in stepwise mann β . However hotfi the steps can possiWy occur in a concomitant fashion to release both the dnigs strauitflæously.

As illustrated in Scheme M3 and M4, Linkers may have additional spacer groups between one side (or both sides) of the liakers and the drug molecule and \$<we of these spacer groups may be deaved independently by a chemical or enzymatic process to release the drugs prematurely before the cleavage of disulfide linkage. The prodrugs and

mutual prodrugs containing such spacer groups may be useful when faster release of dmg(s) is desired.

LISTS OF CANDIDATE DRUGS USEFUL FOR PRODRUG SYNTHESTS:

Drags listed in the following list can be converted to prodrugs of formula I This list is *W* no way limiting the scope of drugs covered in this invention, but given as representative examples. AU the amino- (mcUiding araide-NH and suJfonamide-NH, earbamate-NH, sutfemate-NH, hydrazone-NH, s^carbseone-HH, thios βmicarbazone-NH, wea-NH, phosphoramide-NH and the like. See above, for the description of "amino-containing drugs"), carboxyl-, hydroxyl- ξncliiding oxime-OH), and catfjonyi (both aldehyde and keto groupsycctøtaming dtugs under various therapeutic categories as listed in Merck Index (13th editions) and other daja bases such as prous science's βnscanble, mtegrity and the like and also all the qualified (i,e. amino-, and /or hydroxy.-, and/ot carboxyk and/or carbo Oyl-containing) investigational drugs as listed in databases such as Metck Index. (13^ editions), iddb, ensemble, integrily^ and the like, are coverol under this invention wiUiout any limitation.

ANTI-INPLAMMATORY DRUGS;

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Hydroxyl-coj Λ aiï-ing: 21-Acetoxypregnct toløne, Alcloroetasoue- alfe-Bisabolol, Budesowdc, Deflazacort, Difloiasone, Desonide, Desoximetasone, Diflioxasone, Difl Ω cortolone, Difløprednate, Ditaw \ddot{i} , Flwazacort $^{^{\prime}}$ Fluocjaonide. Flwcoftin Butyl, Flupred $_{f}$ idene Acetate $^{^{\prime}}$ Glucanietaci π , Haleinottide, Halobetasol Propionate, Halo $_{ff}$ etasone, Halopredone Acetate, Ibuproxam, i Λ teprednol Etabonate $_{f}$ Mazip \ddot{i} edone, Mo $_{H}$ tetasone Fufoate, Oxyphenbutazon β Perisoxal, Rimexolone.

Hydjrøtyl-, and Aπúno-containing (including Amide I<IH and Sulphonatn ide KH and Phosphomide IS(H, etc): Bufexatnac, Etofenamate, Fejwcadinol, Ibupipjiam, Isoxicam, Lornoxlcani, Meloxica ή, Oxametacine, Pjroxirøm, mάTenoswarø.

fiydr Üxyl- aad sulphahydiyl-containing: Tjxocortol.

Carboxyl- and Amino-cont &iiÚng (iÏtøludiOg amide NH and sulphonamicto NH andphosphomideXH setc): AcecJofenac, Alirtinop iofeo, Axitienac, 3-Ajwino-4-,

-hydroxybutytic Acid, Carprofem, Diclofenac, Etticnamic Acid, Etodolac, Fhifenaroic Acid, Meclof Ónamic Acid, Mefenamic Acid, Mfhimie Acid, and Tolfenamic Acid.

Carbosyl-containing: Acetnetacin, Acetamidocaptoic Add, Bemdazac, Benoxaprofen, Bettmoprofea, Bucloxic Acid , Butibirfen, Cimnetacra, Clidanac, Clopitac, Feibinac^ Fenbiiien, Fenolozic Acid, Fenoprofen, Fe»tjazac, Flurøxaprofea, Ï l Ω Ibjiprofea, Ibiipwfen, Indomeflia,cin, feofezoko, Iscrø Π pac, Ketopiofen, Lonazolac, Loxoprofen, Metia^iide Acjd, Mofezolac, Naproxen, Oxapfozin, Pirazolac Λ Pir Π rofen Π Protizi Π ic AcJd Π Sulindac, Suprofen, Suxibtizon Π Tiaprofenic Acid, Tolraetin, and Tropesin.

Carboxyl- and Hydrosyl-containing: Balsalazide^ Ettoxolonfe, $F\beta$ ndosal, Olsalazitie^ Oxaceprol, and Ximoproferu

Amino-. Carboxyl- and Hydrøjcyl-eontait ώig: 3-Amino-4-hydtoxybutyric Acid,

Mesalaminc, and Sulfasalazine,

Keto-containtig: N-ibumctoae, and Piketoproftn.

Carboxyl- £md keto-coistiamug; Bermoprofen, Bucloxic Acid, Igoxepac, K.etopiofe π_i , LGxoprof $\beta\alpha$, and Zaltopiof β_{iv}

ANALGESIC AND/OR ANTIP \ddot{I} KE π C DRUGS:

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Atnino-contaiftiog: AminocMoiiheitioXarf\ Aminopropylo π, Aniloddine, Antxfffenio,e, Benorylate\ Bβnzpipetylofl, p-Btomoacetanilide, Butace ω), Carsalam, Difenamizolft, Etersalate* Ethecnzamide, Ethoxazeoe, Flipirtiae Isodixin, Nifenazone, Phenacetin, Pfoβnazopyridioe, Phenocoll, Phenopyrazone, Pianinodine, Piiitramid\ Picopacetamol, RattufenazOftβ Pipetylone, Salveirinβ and Tinoridine.

HydroxyL-coπtainiπg: Benzylmorpinne, Aluminium bïs(acetylsali«^late), Bupr Battorphine, Butoiphanol, Chlorøbulanol, Desomoiplune, Ciiaroaiiol, Codeine, Dihydtocodeitie, Dihydromorpbi π_{e} , D&ydroxyaluminwn acetylsalicylate, DimepHeptaQol, Epta2odnc^ Bthyltnorptiine, Eug ntol, Hydroxypethidiae, Lev«rphaool, Phenazocine, Meptazinol, Metøocin Q Morphine, Nalbuxphine, Pentazocine, Phenoperidine, PhMytsalicylata, Salicin, Ttamadol, and ViminoL

Carbojcyl-eOatainixig; Acetylsalicylsalicylic acid, AlclOfenac, Aspirin, Benoxaprofen, 5-BromosalicyJic acid acetate, Ciqchophen, Diacerein, Dipyracetyl, Fosfosal, Ibufiaiac, Moprofen, and Salicysulfhric acid.

Ataino- and Hydra φ I-eontaifljtøg: Acetaminophen, Acetamlnosalol, Bueetin, Capsaicins, Pezociae, Floctafcniifø Glafenine, Jsoiadol, p-LacfophenetJde^ Norievo φ hanol, Noπnorphi αθ, PhenylrainidD Ï, Salacetamicte, and SaKcylaraide.

Amino- and Carboxyl-comtaining: Actarit, BunifldJizone, CloTuxiO₃ and SaJjcylamide O-acetiic acid.

Carboxyl- and Hydroxyi-containing: Diflut ÓsaJ_s Gentisic acid, and Salsaiate.

10 Keto-oojitaining: Atntolraietin, Dipipanc (2)e, Hydrocodone, Isomethadone, Methadone, Koipipanone, and Phe Oadoxone.

Hydroxy- and Køto containing; Hydromorphone, Ketobemidome, Metopon, Oxycodone, ajttd Oxyxnoiphone.

Carb Oxyl- and Keto-containing: Clometacin, Ketorolac, and Zomepirac.

Amino- Carboxyl- and K β o-contaidngr Bromfenac.

ANTIHYPERTENSIVE DRUGS:

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BethaoidM B Amino-containing; Alfbzosin, Benzylhydroohlorothiazide, Budralazin β Ciclosidomine, Clonidine, Clopamide, Bopmdolol i Bunazosin, Cyclopenthiazide, Dehrisoquiu, Ed^erpidine, Diazoxide, Dihydralazm B Doxazosin, Gwanazodiae, Guanethidin E, Guanochlor, Eudmla ≤ne, GUanabenz, Guanaclhie, Guanadiel, Gua Of βditte, Guanoxa π, Hydracarbrøne, Hydralazine, Hydrofloroethiazide, -hdapaaiide, Iπdojranώi, Irbesartan, Ketanserin 5 Lofexidine, Mebutømate, Mecamylamine Methyl 4-pridyl ketone thiosemicd Wazone, Mib Gradil, Minoxid-l, Monatepil, Moxonidine, phacipfazme, Piπacidil, Piazosiπ. Raubasine, Resciiraamioe, Reserp Üine, Reserpi π e, Rilmciiidine, SyrossiOgopine, Tasosaitan, Terazosin, Tiam Btidine, Todtalazi πe. Toloπidke, Tripamide, mά Ürapidil.

Hydroxy-eontsjxung: Ajmaliiæ, Cicletanme^ Levcrorøakaljm, Nastopidil, PhenactnOptniüti chloride, and Protoveratrines.

Catboxyl-containing: Epros-trtan, Fosinopiil, and Tetanisartaa,

Amino- swil Carbosyl-containing: Al^cepril, gama-Aroinobutyric acid,
Ben£jepril, Caixdcsartan, Cannox,inole, Cawnapril, Cilazapfii, Delapil, Enalapril,

Enalapfilat, Imidapril, Lisinopril, Moexiprjl, Moveltipril, Perindo ρril, Quinapril, Ramipril, Stasia, Spirapril, Teraocspril, Ttandolapril, and Valsartan,

Amino- *mi* Hydro χyl "contώnmg: AcebutoH AlprenoH AmosulaJoJ, Arotinolol, Atenolol, Betaxolol, Bisoprolol, Bosentan, Bucindolol, Bufeniode, Bunitrolol, Bupranølol, Butofilolol, Cadralazine, Cβziprolol, Carazolol, Carteolol, Cetamolol, Carvedilol, Epa colol, indenolol, Nadolol, Dilevalol, Fenoldopam, Guanoxabenz, Labetalol, Losartan, Mepiudolol, Metipra πolol, Metoprolol, Moprolol, Nebjvolol, Olmesartan, Oxpt βaoJol, Penbutolol, Phentolamine, Pildralazi πe, PMdiolol, Propranolol, Rescunetol. Sulfinalol, Talmolol, Tertatolol, Timolol, and Trimaz Osin.

Aitiitto-, Hydroxyl- and Carboxyl-contai Ting: MeUiyldopa, and Sampatrilat, SiilMydtyl-andCarboxyl-coiit-uning; Captopril, aadOmapatrilat, Carbonyl-containirag; Araaidipine, and Epleireiione, ANHBIOTICS:

AU Hie knowni amino-, hydroxyl-, and carbosiyl-coi@alning antibiotics such as Amoxicillin, AmpiciUin, Olivanic acid, Metronidazole, and the like; as listed in Merck Index. 13th edition and other drug databases integrity, ensemble, iddb, and úc like. These antibiotics can be used in combination with beta-lactamase inhibitor such as elavulanic add, peniciUinic acid sulfonc and the like. The following lists of antibacterial ønd antifungal agnets are given for clarity.

20 AK ΠBACTEWAL AGENTS*.

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Ammo-containing: Ac Blapsone, Acetosulfou Bsodium, Ambazone, Bacampicillia, Benzylsulfemide, Brodimoprim, Cefcapene pivoxil, Ce odoxime ptoxetil, Chloraraine-B, Ciilorami πe-T, Caprcomycin, Clofazimine, Cyacetacide, Cycloserine, Düpsoae, Ethionamide, FurazoKurø cMoride^ N2-Fo Tnylsulfison «dine, Puronaade^ Isoniazid, Lenampicilli B ^-(^d^lwlfamoylJsuIfanilaniKcie, LmezoHde, Mafeoide, Moii)haza«amtde, NLturadene, Nitrofurantoin, PenamecilHn, Penethatnate hydriodidø, Pexiganan, PivampiciHin, Pivccfalex Ú, Pidoxydinte, protionamide, Pyxazinamide, 4'-Solasulfone, Subathii∞iOe, 4,4'-Sulfinyldiamli π\ Sulfoxone sodünm, Sulfanilylsulfanilarøidc, Sulfo Tiazide, Sulfabenzamid B Sulfacetamide, Sulfødim Bhoxine, Sulfaciiloipy π dazine, Sulfecytia β Sulfediazwie, Swlfadiciawide, Sulfødoxrøe, Sulfeethidole, Sulfaguanidra \(\beta \) Sulfaguaaole, Sulfetene, Sx/Memefazin B,

Sulfameter, Sulfat&ettødtte, Sulfaaietliizole, Sulfamethomidine, Sulfamethoxazole, Sulfamethoxypyridaz ισε, Sulfamethylthia^le, Sulfametrole, Sul&midochrysoidi πε, Sulfamoxole, Sulfonamide, ρ-Sulfaπilylbenzylamine, Sulfanilylurea, N-Sulfani ιγl-3 4" xylatnide, Sulfaperine, Sulfaphenazole, Sulfaproxyline, Sulfapyrazine, Sulfasoimzole> Sulfasyrnaziπe, Sulfetøiaz σle, Sulfathiourea, Sulfisomidine, Sulfisoxazole, Sultamicillin, Sulfatolamide, TalampioilliD, Taurolidine, Tetoxoprim, Thiazos Ufone, Thiacetazone, Tiocatlide, and *Trimethoprim*,

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Hydroxyl-containing: Azithromycin, Chloroxylexiol, Chlorquinadol, Clofoctol, Cloxyquie, Diathymosulfone, Glucosulfone sodium, NMttp^jrinol, Nifortoinol, Nitroxoline, Roxarsone, Rojcitbfomycin, Xanfliocillm, and Xibotiiol.

CarboxyL-containing (mcludUig sulfet β, phosphate and phosphojjate-containing) !
Amdinocilllin, Cm α caci α Difloxacin, Fosfomycin, and Hydti catpic add.

Amino and Carboxyl-containing (including sulføte-, sulfonic acid-, phosphate and phosphonate-co, taining): Acediasulfone, Amphomycin, Ampidllra, Aiddocillii, Balofloxacin, Betaraipron, Ca^l brøicilHn, Azheo ram, BaciUacin, Cajinda illin, Carumonam, Ceføcloj, Ceńzcdone, Cefazolb, CetfiaWta, Cefditoren, Cefepime, Cefetamet Cefixime, Cefineuoxime, Cefiaetezole, Ceforanide, Ceforanide, Cefotaxime, CdFotβan, Ccfotiam, Cefoxitin, Cβozopran, Ceφ itnizole, Cefpkome, Ceß oxadine, CeModin, Ceftaaidiroe, Cefteram, Ceftezole, Ceftibnten, Ceftixoxime, Cefttia $_{K}$ on $_{B}$, Cefoioxime, Cefitzonam, Cephac β til β sodim π , Cephal «d π Cephaloglycto, Cephalosporin C, Gephalothin, Cephapitin sodiao, Ccphmdinc, Ceph_a loridinc CUastatin, Cip, oflaxacm, Clmafloxacm, Clometoc OBn, Cyclacilto, Didoxacillm, E_f oxacin, Epicillm, F^hb &mcilliπ, HoxadUto, HetecUlH Loracarbef, Metampidll in, MethioUK MezlociUii., NafcUltn, Nopiys Offemide, Opimazide, Oxacfc PeπciHrnCs), PhetiethicUl^ phthalylsulfecetømide, Phthalylsulfethiazole, Penimepicyclme, Piperacillio, PrøpicilHn, Qua** SuccinylsuIfaUdazole, Succisulfone, Sulbenicillm, Sulfechtysoidine, Sulfenilic acid, Temocilliα Ticateilliπ, and Tigemonam.

Amino- and Hydroxyl-containbg: Amikacin, p-Aminosalicylic acid hyd azlde, Arbcka_piπ, A_ή ἀmSet ἀcol, Bambeπnyciπs, S-BromosaKcylhydtoxamic acid, Butirosin, Clindamycin, Clomocyclme, Chloramphenicol, CtocilUn, Colistin, Demeolocydino, Deoxydihyd^streptomycm; Dib^acin, Dihydtostieptomycm, Dixithromycin,

Doxycycline, Enviomycm, EthambutoL, Forimicjas, Genteroycfo Olyconiazide, N4-beta-D-Glucosylsulfa πilatnid β, Gra_nicidm(s) 3 Isepamicin, Kaπamycin ζ), Lkcomycin, Mectocyclrøe, MethacycHne, Micronoij-icm, Neomycin, Netilmicin, Novobiocin, Paromomycin, Phenyl aminosalicylate, Pipacyclme, Polymyxin, Primycin, Ramoplanit*, Ribostainycin, Rifabutin, Rifalazil, Rifam ide, Kifamycin SV3 Riampin, Rifape Otlne, Rifaximln, RiStoCeUn4 Salina2id 2 Smacycline, Sisomicin, Streptolydigin, Stceptomycin, Streptotsticozid, 2-p-Sulfa πlylajjilinoethanol, Thiamphenicol, Thiostrepton, Tobramycin, Tuberactinomycin, Vioraycin, and Virgimamycin,

Hydroxyl- and Carboxyl-containi πg (including sulfate, phosphate and phosphoïiate-contajoing): Fropenem^ Nadifloxacin, Biapenem, Fusidic acid, and Merbrømin.

Hydtoxyl- said Aldehyde-containing: Josajnycia, Leucomycins, Midecamycins, Miokamydn, Rokitamycin, and Spicamycin.

Am»»o- $_3$ Hydroxyl-, and Carbon-containing (including sulfate, phosphate and phosphonate-conteining): p-Ami π osaltcylic acid, Apjoyclime, AaiOTficillio, Apalcillin, Aspoxicilli-t $_j$ B β ozoylpaS $_j$ Cefadtoxil $^$ Cefemandole, C β fatrizhe, Cejfbupera2one, Cefdinir, Cefininøx, Cefouicid, C β fop $^$ ra $^$ one, Cefosdis, Ceftwiiatt-i $^$ i β , C ϕ rozil, Eriapeticm, Flomoxef, Imipen β m * Lym $\dot{\phi}$ cycline, Meropenet π , Moxalactam, Ncgamycin, Panipenem $^$ Ritipenem, Salazosulfadim idine, Sul α lojdc acid, 4-S α lfanilam idosaiicylic acid α 0 Te α 1 Te α 2 Te α 3 Te α 4 Vancomycin.

Keto-contai ϊώis: Tioleandomycin.

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Hydroxy- and Keto-containing: Carbotnycin, Clarithromycin, Erythromycin, ali erythtomycitt ester derivatives. Oleandomycin, and Telithromycm.

Hydroxy *, Aldehyde-, and Keto-conta» ω jg: Rosaramici π .

25 Amino- and Keto-containing: Porfjromycjn-

Carboxyl- a α t Keto-containing: Fleroxac \ddot{u} t, Flumeq \ddot{i} iinc, Miloxadn, Nalidixic ac \ddot{i} d, Ofloxacin, Oxolinic acid, Pefloxacin, Piromidic acid, Ptulifloxadn, Roso $^{\beta}$ tø, and Rvfloxacto.

Amino-, hydroxyH and Keto-containiug: Cblortdtracyclkie, Dalfqitistra,
 Guamecycltøe, Mikamycin, Minocycline, Oxytetracyclrøe, Piistinamycm, Quinupristin,
 Rolitettacycline, Spectino πiydift, and Tfospectowtyckn.

Amino-, carboxyl*-, and Jketo-containing: Gaienojcactø, Gatifloxaoin, Gcmifloxacio, Orepafloxacia, Lotnefl Oxadn, Moxifloxacin, Norfloxacin, Pazuiloxacin, Pipemidio acid, Sitafloxacin, Sparfloxacin, Tosufloxacio, and Trovafloxacin.

Sulfehydryl-cotttaining; Pjrithiotte.

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ANTIFUNGAL AGENTS:

Attiino-containing: Chlordantoi π , Exalamid β , Flucytosine, Loflucarba Λ Magenta Is and Pyirolnit)dn.

Hydroxy-coiitaining; Cblorpliiβnesi π, Cid,op ii»3i;, Dermoatatin, Filipin,
 Fhicomazole, FuAgichroffito, Pecilocin. Posac Chazole, Ravuconazole, Rubijervine,
 Siccat Ún, 2,4,6-Ttibromo-TO-ctesol and Voriconazole,

Cïffboxyl-iiotiteúxùig: Undecyleaic acid (KMffidecenoic acid), and Propionic acid.

Amino- and Carboxyl-contain Óngt Azaserine,

AflO'mo- and Hydroxyl-containing: Salicylaailide, AcriiSorciDi (9-Aminoactindine coiøpoufld with 4-Hexylresoroinol (1:1)), Anidulafungin, Bromosalicylchloianilide, Bnclosamide, Caspofangin, Micafimgin, and Tubercidin.

Aroi π_0 -, Ca Λ oxyl- and Hydroxyl-contain ling: Natamycin, Amphotericin B, Lrøensomycia, and Nystatin.

Carboityl-coutaiiing: sodinm propionate and griseof Civia.

20 Hydroxy- and carbonyl-containing: Vitidin.

Amino-, hydroxyl-, a Of carbonyl-contauraig: PeTtmycin and Me5partdc«x.

Amino-, cwboxyl-, hydroxy!-, and carbonyl-containiBgt Candicidin.

ANITVIRAL PRUGS:

Hyd ï oxy-containing: Edojtudine, Floxutidine. Idoximdine, Kethoxal ,

25 Pod Phyllotoxin, Sorivtidroe, Stavuduie, Triflmidine, and Zidovudine.

Atevirdin B Afflidinoinycjn, Capravuing, Amino-c Ontai Tung: Amantadine, toaquimod^ Lamivudiiaei Delavirdinc, Efavirenz, Famciclovir, Methisazone, Stallimycin' roantadme, MoioTcydine, Nevimpine,, Oseltamivir, Rimantadine, Valacyclovir.

Amino- and Hydroxyl-comaining: Abacavir, Aftycd Ovir, Adefovits, AmF ei **av fr>
Atazanavir, Cidofovir. ÜMdanosine, Didc Osya Óenosfene, Emt Ócitabiae, Entecavir,

Indinavir, Lamivudke, kopjnavir, 5-(methylainino>2-deoxyuridin,e (MADU), Nelfmavfr, Penciclovir, Resiquimod, Ribavirin, Ritonavir, Saquinavir, Tenofovii, Tipranavir, Valganciclovir, Vidarabine, and Zajcitabine.

Carboxyl- and HycLroxyl-contaiting: Foscarnet sodhrø, and Ganciclovir.

5 Amino-, Carboxyl- and Hydroxyl-contøirø Og: Zanamivir,

ANTIMALARIAL:

Amino-c Catai πιπg; Chlorguanide, Chloroq Une, Chlorpioguanil, Cycloguanil, Pamaquine, Pla ÜΛocid, Primaquine, Quinocid β and Tafenoqia πε.

Hydroxyl-contai π ing: Artemisini π alcohol, Bebeerineg, Cincljonidin β Cinchonine, Dihydbroartemisinii^ Itelofentdjie, Luteiefentrioe, Quinine and Yingzhaosui A,

Carboxyl-co Caiaiag: Arteflenc and Artesuaate.

Amino-, and Hydroxyl-containing: Amodiaquin, Hydroxychloroquine, Mefloquine, and Pyronaridine,

15 Hydroxyl, and carbonyl-containing: Fosmidomycin.

Catbojoyl-contaitwig: Arteflece,

AK ΠΝΕΟΡLASTIC PRUGS.-

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HydrOJRy-contaJniog: Acladnomycins, Arzox ifeπe, Batimastat, Broxmiditt β Calusterone, Capecitabine, CC-1065, Chroraomycins, Diethyi\$tilbe &rol, Docetaxel, Doxifluridine, Droloxifene, I>romo9tanolone, Enocitabine, Epitiostanol, Estramustin^ Etøntda2ole, Etoposide Feπretkude, Ftøvopiridol, Forjπestane, Fosfestrøl, Fulvestrant, Gemeitabine, Irinoteca α Mel^gesttol, Mβaogaril, Miltefbsine, Mitobionttol, Mitoïaetα, McDidamol, Njtracrine, Nogalarayci^ Noπ-jhydroguaiardic Add, Olivomycins, Pacljtaxel and other known pacHtafeel analogs, P^camycin^ PodophyHotoxin, Retinoic acid (including all ttans-retinoic acid), Roqtiinim, Rubiteca π, Seocalcitol;, Temop offin, Teniposide^ Teπuazonic Acid, Topotecan, Valrobieitt, Vinblastine, Vincristine, and Losuqvidar.

Ammo-containing (including Araide-NH abd S«I ρ hojiamide-NH $_{7}$ Carbt Chate>NH, Sulfømafe-NH, and Phosphomide-NH): D-Aminocainptoiheciti, Aminolevulinic. Acid, Amsacri π e, Bisantrene, Cacti π omycin, Carboquone, C \propto ino $^{\wedge}$ CamMistine, Cyclopkosphanaide, Dacarbazane, Dadjaomyci $^{\wedge}$ Demecolcine, Piaziq,u Θ i $^{\beta}$, 6-IMazo-S-

(DON), Edattexate, Efaproxiral, Eflornitbine, Enitøracil, Etlotinib, oxo-L-aorleuctøe Fluoroiuracil, Gefifcinib, Gem atabine, Goserelin, Histamine, Ifbsfamide, Iraatitiib, Improsulfan, Lanreotide, Leuprolide, Liarozole, Lobaplatin, Cisptetin, Carboplatin, LoITiUSUile, Loft-rfar Tib, Marmoniustine, Melphalan, Methotrexate, Methyl Nilutwitid B hTunustine, Amiuolevulkate, Miboplatin, Mit Quazone, Mitoxantrone, Nolatreaed, Oxalipla ώi, Pemett&xed, Phetiamet, Pmtrex Ún, Procarbazine, Raltitrexed, Tariq Udar, Temozolomide, Thiamiprine, Thiogua πιπε, Tipifamib, Tirapazamine, 3-Aminopyridi Ot-2-ca3rbo Xaldehyde iMosemicarbazø»e (3-AP)/S-Aminopyridine^-(3-AMP/Triapjne /OCX491/OCX-0191) methyl-2-carboxaJdehyde ftiosemicarbazone Trimetrexate, Uracil Mustard, Uredepa ([Bis(1-a2iridinyl)phosphinyl3caibaxcdc acid ethyl ester, ethyl carbamate andMctøedepa.

Bodh Hydroxy- & Amino- containi lig (including Axnide-NM ajid Sulphonamide-NH, Catbamate-ISfH, Sulferoat BMH, and Phospho TUCONH): Ancitabine, Anthramycin, Azacitidine, Bleomycins, Blopirimine, Busereliit, Caribiciny Chlorozotocin, Cladribin β Defos&mide, Docetaxel 5 Doxorubicin, Cytsrabine[^] Daunorubicin, Decitabfoc, Ect Boascidin S. Epirubicin, Oemdtabine, Hydroxyurea, Idarubicin, Maritnastat, 6-Mcrcaptopurine 2 Pfetitostatin, Peplomycin, p B fosfemide, Pirarubicin, Prinomastat^ Ranimustin β , Streptonigri π Streptozocin, Tïazofiiriti, Troxaoitabine, Puroroyciti, VindesStiBand Zorubican.

20 Carboxyl-cont ώ-ing; Butyric acid-AKHOXIDANTS/FKEE RADICAL SCAVENGERS;

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Amino-cotttait ώig (including some investigational diugs): B1X-51072 (4,4-dimethyl-3,4-d^ydro-2H-1,2-bfiji2ose]l-aia2ine), Carnosme, Mdatom (+>-R-Piamip εx σe, and Stobad ine.

Hydroxyl-c Ontainii Q O^^dws some inveatigationd drags): Ascorbic add, Cu_t cumin, Dexanabi ποi, Edaravon, (-) Epi^allocatediin Gallate, Emoxipin, Hydioxytyrosol, Idebenone, Luteolin, Nicaaartine, NZ-419, Oxyresverattol, Probucol (itjcl Udi Üg probucol prodrugs such as AGI-1067 and AGÏ-1096), Querc βtin, Reductic acid, Silybixy Tempol (4-Hydroxy-TEMPO), and a fa-Tocoplie l'oi (Vitan Ú iE).

Carboxyl-containing (including some investigational drugs); N-Acetyl L-cysteme,
Alfa-Lipoic acid, Rajjofelast, and Tetoiï-ilasL

ArainoVHydrøxyl-, and Carboxykcontainrag (including some investigational drugs): N-Acdyl earnosine, ^Carnitine, and SCMC-Lys (S-carboxy Tuethyi-L-cystcine Lysine salt H2O).

Amino- and Hydroxyl-containing (including some investigational drugs): BN-82451, and Zeatui.

BIN ZODIAZEPINE TRANQUILIZERS AND HYPNOTICS:

Diazepam, Triazolam, Alprazolam, and the like,

ANTIULCERAOENTS:

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A Thi-io-co That fing (including Amide NH and Sulpfoojianiide NH and Phosptøtnide NH, etc): Aldioxa, Benexate HCl, Citoßtidine, Ebrotidke, Ecabapide, Ïrøogladiπe, Laj&itjdine, Lansoprazole, Esaprazoie, Esomeprazolc, Famotidine, Ranitidine, PøfttoOtazole Pitc Tziqjine, Pol^preidnc, RabeprassoK Omepiazole, RoKatidine, and Tfoxipida.

Hydroxyl (and Keto a/d Keto and/or Carboxy]) -containing." Exprostil, 15 Misoprostol* Omoprøstfl, Plautiotol, Bioprostil, Tramoprastit, and Qryzanol A.

Carboxyl-contaioing: Acetoxolone, Carbenoxolott B Rebamipide and Sofalcone.

Amino (or Hydroxy.) - and Catboxyl-cofttaitwng-' Cctrajeate, Ecabet, S-MetHylmethionin^ RosaprostoL. and Rotraxate.

Carbonyl-contaaiing: Spj2ofiirone, and Tepre ToOe.

20 ANHCONVÜLSANTS;

Amino-contaitra \(\beta \) (including Amide NH and S\(\phi \) bonamide NH aad Phosphoioid© NH, etc.)- Acetylphenet Wide, Albutoin, iV-benzÿ-3-chlorop Topio Tamide, Cayba_tnazepine; Cinromid β Clonazepam, Decimemid β Dimethadione Doxcnitoin, Ethoauximide, Ethortoift, Felbamate, Fosplieiiytoin, Lamotrigine, Leve Üracetaiπ Mephcnytoin, Mephobarbital, Meti iarbiH Methctoiπ, Nitrazepam, Oxcarfcazepitøe, Phenacewid β Phctoefljarbital, Fhenctoride, Phenobarbitad. Oη c ω axmzepiùe, Phenylmcthylbaibituric Acid, Phenytoro, Phethenylate Sodium, Primidone, Progabide, Remacemide, Rufinamide, Suølofenide, Sultiliame, Talampanel, Tetrantoin, Tojrømate, Valpfomide, Zonisamide, 5-Methyl-5-(3-phenanifaiyl)hydaÜtoin, and 3-Methyl-5phenylhydantom.

Hydroxyl-containing: Ganaxoloiie.

Hydroxyl-, and Atmno-contai Omg {including Amide NH and Sulphonaiaide NH and Phosph Omide JSIH) 4-Aaino-3-hydroxybutyrfc Acid, Atrolactamide, and Buramate.

Carboxyl- and Arøïm»-Contaming (iπdudiiig Amide KH and Sulphonaraide NH and Phosphomide NH): Gabapentk, Pregabalfa, and Vigabatri π.

Carboxyl-containing; Tlagabine, and Valproic Acid,

ANTIPAJRKINSON'S: Levodopa & Carbidopa.

ANTIDEPRESSANT:

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Ami Oto-contaiting (including Aft Úde IsIH and Sulphonainide NH CatoxaSiOpe, Deanejciptiline, Desipramme, Phosphomide NH₅ etc.): Amoxapine, Duloxetine, Httoxetine, Fluvoxa Tiine. Indalpine, Indeloxazrae Hydrochloride, iproclozide, Ipp niazid, Isocarboxazid, Levophacetopeiane, Maprotttinc, Metapramme Mitoaci Oran, Muiaptiue, Moclobemide, Nialamide, Nomifensine, Nortriptyline, Octamoxi π , Oxypetim, Paroxetine, Prot ϕ fylme, Reboxetiue, RoKpram, S β tmlin β Tofenadn, Tfanykyp«>ni»n e Viloxazine Bemoxtoe, and R Gicyprine.

Hydroxyl-contai π ing; Befloxatone, Bupropion, Fenpentadiol, Hypejicin, Opipramol, Pyrisuoc \ddot{i} deanol, Toloxaton β and Ventef-fl-ine.

Hydt Oxyl-, and Aroino-oontaining (including Amide NH and Sulpfeonamide NH and Phosphomide NH)? ^Ade ObsylmctJiio π ine, 5-Hydroxjrtiyptøpfc9% and Roxiødol β

Carboxyl- and Amino-Co- α aining (incltiding Amide NH mi Sidphoaamfcfe NH and PhoFphomide KH): AttMneptSne, and Tiatieptine,

ANT HISTAM INtC

Atamo-co Haini π_g (including Amide NH and Sulphonamide MH a Cd Phosph Cmide NH, etc.): Antazoline, Astemi-Mlc, Clobepzepam, Deslorated Úie, Epinastine, Metron S»Mtrølastiw β , and Tritoqualine.

Hydroxyl-containing; Terfe Tadine, and T'Hydrox-yeihylpro Tyiethaane Chloride.

Carboxyl-containing; Acrtvastine, Bepota\$tine, Cetirizine, and Levocabastine, Catboxyl- andHydroxyl-contai Tung: Fesofeiiadine.

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ANTICANCER, ArøOxmA ÏTVB, ANTnNFLAMMATORY 5 AND CARDIOPROTECTIVE AGENT: Trans-Resveratrol [(EJ-S^\'\^-tdhydrøjtystilbeoe), ANTIDIABETIC: Metformin, and Nategljjude/GHpizide/Glibenclajnide (\$\beta\$ lybmi\artis).

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It should be understood that while the lists of *names* of various categories of drugs have been included above, such lists \$ra presented in a way of illustration of the structural features of the qualifying drugs in this invention and therefore, the number and types of listed drugs are not necessarily limited; thereto. In principal, any amino-, and /or carboxy], and/or carbonyl-, and/or hydroxyl-containing drug (from both lenovm and irtvest.gatioi.al drugs), irrespective of its therapeutic category and their mechanism of action, as listed in drug databases such as Merck Index, prous science's ensemble, integrity, iddb, and the like, are generally covered within the true spirit and scope of toe present invention. For clarity, in addition to the above lists of drugs, any amino-, and/or carbosyl-, and/or carbonyl-, and/or hydfoxyl-containing drugfs) (both *known*, tod investigational drugs) from the following therapeutic areas are covered without any limitation:

CENTRAt NERVOUS SYSTEM: Sedatives, Hypnotics, Antidepressants, Antipsychotics and Antimonies, Analgesics & Antipyretics* Antimigraine agents, Anticonvulsants, Drugs used in parkinsonism and movement disorders, Drug for dementia, Antiemtics, drugs for Vertigo, CNS Stimulants & activators.

EYE: Antiinfective eye preparations, Antiitaflairmatory and antiallergie preparations, antiglucoma drags and other preparations o cue eye diseases.

EAR, NOSE and OROPHARYNX: Drugs used aural, nasal and otopharyngeal preparation.

CAFDIOVASCULAR SYSTEM; Antiattfcythcmic drugs, Antihypertensives (including alfa/bBta-blocfccrs, channel blockers^ ACE inhibitors, Angiotensin II receptor antagonists, diuretics, etc.), Antianginals (including nitrates, calcium channel blockers, etc.), Drugs for cardiac Mure and shock, Vasodilators, Coagulants, AnticoaguJmits, Thrombolytics and antiplatelet drugs.

RESPIRATORY SYSTEM: Respiratory stimulants. Antitussives, Expectorants, Mucolytics and Decongestants, Antihistamine agents, and antiasthmatics.

GASTRO INTESTINAL TRACT: Antiulcer and Antisecretory drugs (including H_i receptor antagonists, Ptotoa Pvanp inMbitors, Prostaglandin analogues, etc.):,

Antacids, Antispasmodics and drags modifying intestinal motility, Antidiarrhoeals (including antimotility and antimicrobial drugs) mi drugs acting on gall bladder.

GEMtO URINARY SYSTEM: Urinary autiiπfectives, Diuretics, Uπaary analgesics & antispasmodics, Ant ππfective drugs acting on uterus. Drugs for prostatic hypertrophy (including alfa blockers and antiaadrogens), Drugs for erectile dysfunction, and Spermicidal & nonhom Onal contratceptives.

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SKIN: Emollients and Jsetatolytics, topical antiinfectiv β_s ; topical antifungals, topical parasiticidals, topical steroids, topical drugs for acne vulgaris, drugs for psoriasis, pigmentation disorders, and Antiscbotthoeics.

MUSCULOSKELETAL DISORDERS; Non Steroidal Anti Inflammatoiy Drugs (MSAIDs) including COX-2 inhibitor Aatiarftø itic agents, —mmunosuppressants, Topical analgesics, Muscle relaxants and Neuromuscular J>rags.

INFECTIONS AND INFESTATIONS: Penicillin antibiotics, CepHalosporin & antibiotics, MacrolWe aoi biotics, antibiotics, Quiuolone Fluoroquinolone Tetracycline Sulfonamides, Autiana Ctobics such as Ctøoramphenicol, antibiotics, Metronidazole, Antitubejcular drugs, AntUeprosy drugs, Antifimgats, Antiprotozoals, Anthelihitithics & Ant Unfestive Drugs, Antunalarials and Antivirals.

ENDOCaUNE SYSTEM: Anabolic and androgenic steroids, Corticosteroids,

Oestrogens, Progestogens and Homional contraceptives, FettiUty Agents. Trophic

fa.oïmones and related <frugs, Thyroid and antithyroid drugs, Antidiabetics and
hyperglycaemics.

NUTIUXION: Vitamin' Amino acids, Anti-obesity drugs

METABOLISM: Hypolipidaemic drags (including fibric acjld derivative $^$ statins [(i.e., HMG CoA ieductase inhibitois), nicotinlG acid group, β tcj, Drags tised for Gout and Drugs affecting bone metabolism (including bisphosplxonates).

NEOPLASTIC **BISOFDERS:** Anticancer drugs such as alkylating cytotoxic antibiotics, antimetabolites such as cytarbtae, Rudarbine, 5-Ftøoxo Vacil. Thioguanine, etc. " Vinca alkaloids and Etoposide, Taxancs, Mercaptopurine, Topoisomeras β \ iid\delta\bitors, Cytotoxic immunosupptessants, Immunostimtdants.

Cytoprotectives such as Ainifostine, O β strogens, Progestogens, hormo π antagonists and other antineoplastic dtugs.

ALLERGY AND IMMUNOLOGY: Antiallurgics such as non-sedative antihistamins (e.g., Cetirfeme $_s$ Desloratadi π e, Terfe π adine, Fexofenadine, etc.), sedative histamines and histaifliflie receptor blockers.

ANAESTHETICS & SWGICALS: Local anaesthetics, intravenous anaesthetics, inhalation anaesthetics and muscle relaxants.

DRUGCOMBINATIONS;

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It is appreciated that prodrugs of any two or more druga fern the above lists of potential drags can be used in combination depending on the medical application/need. While a combination formulation may occasionally consist of more than two drugs (depending on the medical aeed), the following pairs of drugs are covered in this invention as illustrative pairs of candidate drugs for combination therapy.

ANTICANCER: Paclitaxel and Doxorubicin, Pacliiaxel and Mitomycin C; **Paclitaxel** 9-amw ocamptothee6, 3-Amittopyridi π -^2-carboxaldehyde and thiosemicatbazone (3-APy 3-Aminopyridine-4-methyl-2-carboxaldehyde thioseroicarbazone (3-AMP) and another known anticancer drug such as Pacltøel, Doxorubicin, Mitomycin C and the like; CC-1065 and another known anticancer drug such as Paclitaxel, Doxoiubidn > Mitomycin C and the like; "frans-Resvejattol [(E)-S['] iS-triliydtoxystilben β) and another known anticancer dtug such as Pactitax β 1, Doxorubicin, Mitomycin C and the like; Ren'nøic add (including all fcrans-famoic acid) and Butyric acid. Paclitaxel and Captopril, Doxorubicin and Biotte. 5-FluorouiaciI and Cytarabine. Edatrexate and Paclitaxel; Cephalospoianic acid and Paclitaxel; Cephalosporin and Paclitaxel; and Paclitaxel and Geincitabine.

25 ANTIPERKINSON'S: Levodopa and Carbidopa.

AFTIBIO 'H CS: Amoxicillin and Clavulaaic acid; Ampicillra and Clavulanie acid, Amoxicillin and Pencillinic acid sulfone; Ampicittin and Pencilline acid, sulfone; OHvanic acid (or any carbapenern antbiotic) and a renal dipeptidase (dehydropeptidase I) inhibitor such as 3-substiMed Z-2"acylai3Unopropionic acid and the like.

ANTILIPIDEMIC AND HYPERTENSIONr LJflbwl and IL \sim va#ati-i/i>ravasta* luvastatin/Atorvastatin/Simvastatin; Ezetimibe and Lovastati π/Pravastatin/Flwastatin/Atorvastatin/Siinvastat iπ;

Amlodipme and Lovastatin/P*avastatii^luvastatii^Atorva^tijySimvastatut

5 ANTIDIABETIC; Metformin mα Nateglinide/Glipizide/GKbeiiclamide (Glyburide)

ANTIDIABETIC AND HYPERTENSION: Metfbratift and Lovastati T/Pravasiatiti/Fluv.^tatin/Atorvastati-1/S invastatin.

ANTIASTHMATIC, ALLERGIC RHINITIS AND CHRONIC OBSTRUCTIVE

PULMONARY DISEASE (COPD); Psetidoephedtfne and Fexofeinadine/Ce^mine/Deslotatadinc/Epinastine; Salbutamol and Ipratropium btojnide; Mometasone aod F@moterol/Salmeterol; Fluticasone and Fo@noterol/Salmeterol; Budesonide acceptation acceptation.

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ANTIARTHR ITIS, INFLAMMATION AND ULCERS: Diclofenac (any known NSAID) and Misoprostol; Diclofenac (any known NSAID) and a proton pump inhibitor su,cix as Omeprazole, Lansoprazol, Rabepxasol β Lramn Opraz (Te, Pantoprazole, and £he like. A known antibacterial agent and a proton pump inhibitor such as Omeprazole, Lansoprazol, Rabeprazole, Leminoprazole, Pantopra2ola, and the like; Naproxen (or any known NSATD) and Prophenazone; Acetaminophen and chlorzoxazone/iaietaxalane/mepkenoxalone.

ANTIVIRAL (HIV/AIDS, HEPATITIS B AND OTHER VIRAL INFECTIONS): Zidovudine and Lamivucühe-, Triple prodiug of Zidovudine; Lantfvudine and Abacavir (Ziageo,); topinavit and Ritonavir; Lanaivudine and Adefovir or its prodrug adafovir dipivojdl; Amprarøvjr and Zidovudine; Nelfinavix m & a nucleoside revefs β transcriptase inhibitor such as Zidovudine L-anivudine, and the like; Stavudine and an an α tetroviral agem such as Zidovudfai β La π ω vudin β and the like; Dideoxyino $\ddot{\alpha}$ ine and α antiretrovital agent such as Zidovudine α Lamiv α 0 and the Jike; Eratricitabine and Penciclovir/Faracidovit; Acyclovir (or any other k α 0 or antiviral compound) find a bite acid such as oholate, deoxycholate, chenodeoj α 1 cholata, and ursodeoxycholate α 2 targeting bile acid transporters for enhanced oral bioavailability of the drug; Triple prød α 1 g of Zidovudine, kamivudme and Efaviter α 2

 f_i addition to the Above list of drugs, the present invention also covers newer drugs with the above mentioned active fractional groups as listed in the Merck index (13 $^{\Lambda}$ edition) and other drug databases such as Prous Science's ensemble, integrity and the like without any limitation.

It should be understood that either or both of any selected pail of drugg (in any proportion) can be in the fomi of prodmg(s) of formula ϕ or pharmaceutically acceptable salts thereof and the other drug can be in its native form. For clarity, let us assume that Ibuprofen and Paracetamol are present as active principles in a pharmaceutical withposition. Then, either or both of these drugs can be in their prodrug farm (i.e., NO-Parac#tamol and Ibuprofen/ Paracetamol and NO-Ibuprofen/ NO-Paracetam of and NO-Ibuprofen, etc.) and they can be present in any proportion.

It sliould also be understood that a pharmaceutical composition consisting of two or more of the above listed/qualified drugs_s one of the drugs $c\beta t$ be in the form of NO-releasing (mtxowy derivative) prodrug and the other drug(s) b the combination can be in tixe form another type of prodrug®.

It should also be understood that a pharmaceutical composition containing a combination of one of the above listed/qualified Örug(a) and its own prodrug is also covered (i.e., a pharmaceutical composition consisting of NO-Paracetataol and Paracetamol in any propoition). Üt such pharmaceutical coiufeinatiotts, the ftee drug will be useful for faster onset of action and the prodrug will be useful lor extension of the duration of action as H releases the drug in a controlled fashion over * longer period of time. Such combination drag therapy may also niinimize the toxicity and other side effects due to excessive plasraa concentration of free drug. It should also be understood that a pharmaceutical combination ω ay contain a prodrug of one of the above listed/qualified drugs and another type of prodrug of the same drug (>.e., NO prodrug of paracetamol and mutual prodrug of paracetamol with another drag) and these can be present in any therapeutic proportion depending on the medical need.

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EXPERIMENTAL

ABBREVIATIONS USED;

BOP: Benzotriazol-i -yl-o^jty-.r»Xdimethylaniino) phospho ntmr hexafluotophosphate

DMF: N,N"Dimethylfotmamide

5 DSC: N N'*Pisucci πmi<Jyl carbonate

CDl! N^'-Carbonyldiirøidazole

DTE; Dithioetythritol

DTT:Ditiaiothf Btol

DCC: N,N"'Dicyclohexylcarbodiit»ide

10 EDAC, HCl: 1-Ethyi <3-d^e%]|a π-inopropyl)c^bodiimide hydrochloride

HBTU-, 0«(Benzoftta MI-I-y^>N,N N^N^e(Iaffi βilylairo)t^UIαhexafit»ojophosphate

TBTUt O-\$\psi\$ ciKOtriazol-l-yl^N^^N'-tetramd^yl \quad \text{\$\Omega}\$ wnitim tetrafluoroborate

EtOH.' Ethaπoi

Et,O; Diethyl ether

15 THF: Teftahydroftaan

DMSO: Dimethyl sulfoxide

TEA: Tjdlethylamine

DIPEA: N,N-DHsop-t pylcthylawine

DCM: Dichl Gomethane

20 EtOAc: Ethyl acetate

DME; Dimethoxyethane

MeOH; Methanol

PE; Petroleum ether

RT; Room temperature

25 TFA: Twfluorøacetic acid

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HOBT: N-Hydroxyb^nzottiazo Ïe

SYNTHETIC METHODS:

The prodrugs described herein can be prepared by any number of methods knovm/otvious to tiiose skilled in 1hc art. The synthetic approaches and the tøakages are chosen depending upon the ftoOttional groups suck as carboxyl. tøydcoxyl, aa Úao or carbonyl groups piesent h the drag molecules to be used. The Mowing lUustxativ^β

methods, as shown in Schemes 1 through 9, can be utilized to make carbonate, urethane, amide, ester, N-acyl carbamate, N-acyl aroide, N-acyl sulfamate, and N-acyl sulfonamide, N-acyl phosphoramide,, N-øxycarbonylsulfonamide, N-oxycaibooylcarbamate linkages, etc, between drag(s) and linkers).

Methodfs) of making carbonate linkasefs);

As depicted in tie scheme 1, the carbonate linkage between the drug and the linker can be made by reacting the hydroxyl-coRtainiπg drug (alternatively, hydjroxyl group of the linker) with phosgene or its equivalents such as diphosgene, tπphosgene, N₁N) CarbonyldiJrnid-zole (CDI), N₂N'-disuccjnk nidyl carbonate (DSC), 4-nitrophenyl chlorofotmate and the like, to give a reactive alkoxycarbonyl derivative, where LG is suitable leaving group such as a halide, imidazole, O-succh-imide⁴ 4-nittophenoxide and the like, which can he reacted with hydroxyl group of the linker (alternatively, hydroxyl group of drug if the linker is converted to active alkoxyqacbonyl derivative) in the presence of a suitable base and solvent

Scheme 1

Bases such as triethylamke, düsopropylethylamine, 4-(dimethylamino)jpyűdine (DMA?), and the like, can be used. Suitable solvents include CH₂Cl₂, CHCU, DMF, THF, ACN, ethyl acetate, ethyl ether and (he like.

Methodfsi of making methane linkagefe):

As shown in scheme 2, the nrethane linkage between the drug and the linker can be made by reacting * e hydroxyl-contait wig linker with phosgene or its equivalents (defined above) to give a reactive alkoxycaxbonyl derivative, which can fee reacted with amino-contait wig drug in the presence of a suitable base and solvent Alternatively, a verthane linkage can, be made by adding an alcohol to an, isocyanate.

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Suitable bases and solvents are same as defined above.

Melhod fs) of makin g amide or ester Ifokanefs);

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As shown in the Scheme 3, an amide or ester linkage between the drag and the linker can be made by reacting a carboxyl-containing drug with an amino- or hydroxyl-containing linket in the presence of a statable coupling agent, base and solvent Alternatively, the carboxyl-containing compound can be first converted to reactive carbonyl derivative smch as an acid halid β , a succinimide ester, a pentafitioiopheay $\ddot{\imath}$ ester, an imidtiZoHide and the like, which can be treated with amtø σ -contai π ing or hydroxyl-contøiiBiing linker in the presence of a suitable base and solvent to afford the co σ espo π ding amide or ester σ dtage(s), respectively (see, Boda π s Eky, M. and Bodanszky, A, The Practice of Peptide Synthesis, Springer-Veilag, New York, 1984)

Suitable coupling agents include DCC, EDCLHC1, BOP, HBTXJ, TBTU, DCC/HOBT, EDC/HOBT, and the like. Suitable bases and spfvents are same as defined above.

Metfrodfet of making N^acyl.caibamate acdN-acvt urea_linkage:

The linkage such as N-acyl carbamate linkage between the Hinker and dtug c&n be made as sho'vn in Scheme 4, Tlbw, treatment of an alcohol with phosgene or its

equivalent can yield tine corresponding carbonochloridate, which upon treatment vyitfi aittntonia gas can give the corresponding carbamate intermediate. The carbamate nitrogen can be acylated by a suitable carboxyUc acid derivatives such as anhydride or acid halide, a succiπimid β ester, a pentafluorophenyl ester, an iπύdazoUde, and the like, in Hie pïesence of a suitable base to yield the corresponding N-acyl carbamate. Alternatively, N-aoy] carbamate can be made by tiic reaction of am ajcofcol with N-acyl i9ocyanate, which can be prepared either by the reaction of the corresponding amide wth ojralyl chloride (See, Speziale A. J, et al., J. Qrø. Chem. 1962, 27, 3742; SpβzJale, A, J, et al, J. Org. Chβm. 1963, 28, 1805-18U) or by the reaction of the corresponding acid chloride vήth silver cyaaate. (See, Hill, AJ. et al.* J. Am. Chem, Soc, 1940, 62> 1595; Kim, D.K. 1 Heterocyclic Chem. 1995, 32, 1625).

Suitable bases and solvents are same as defined above.

Methods of making N^acvl amide linkage:

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The TSt-acyl amids linkage between the linker and drug can he made as shown in Scheme 5, Thus, the amide nitrogen can be acylated by a suitable carbo^ylic acid derivatives such as anhydride or acid halide, a succinluolde ester, a pentøøuowphenyl ester, an iimdazolide, and the like, in the presence of a suitable base to yfeW the corresponding N-acyl amide.

Rx and Ry are any monovalent organic radicals.

Scheme 5

Suitable bases and solvents are same as defined above.

M^βthodtø of matøflg N-a&yljguflfamatejuj feaggj

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The linkage such as N-aoyl sulfamate between the linker and drug can be made as shown in Scheme 6. Thus, treatment of an alcohol with sulfuryl chloride in the presence of suitable base gives the intermediate sujfocblofidate, which can be converted to ώc corresponding sulfarøate. Acylatiøn of sulfajnat βnitrogen with a suitable Carbojcylic acid derivatives such as anhydride or acid halide-, a succinimide ester, a pentafluoroph βnyl estet;, an imidazoline, and the like, can yield the cojxesponduig N-acyl sulfamate.

Rx and Ry are any monovalent organic radicals.

<u>Scheme 6</u>

Suitable bases a&\(\delta\) solvents are same as defined above.

Methodfs) of ntakinjgN^asyl/oxycarbonyl gdlfonamide linkages:

The N-acyl/oxyoaibonyl sulfonamide linkage between the HTker and drug can be made as shown in Scheme 7. Thus, a sulfonamide nitrogen can be acylated by a suitable carboxylic acid derivatives such as afchydride or acid halide, a socciniraide estet, a, pentafluorophenyl \$ster, an imidaaolide, and the like, to yield the corresponding N-acyls_{ii}lfonamide, which can me metaUated using an inorganic base. Similarly, the

sulfonamide nitrogen can be acylated by a suitable foπnyl chloride derivative such as alkyloxycarbonyl chloride, imidazolide and the like, to yield the coatfsponding N-alkyloxycarbonyl sulfonamide as *shown*, ifl the scheme. Alternatively, the same linkage can be made by the reaction of an alcohol with sulfonyl isoeyanate which can be prepared by known methods such by treatment of sulfonamide with oxalyl chloride (see, Hans Mcalla et at., US2666787 or Smith, 1 et al., I Oxg. Chem. 1965, 30, 12604262) or by treatment of sulfonyl chloride with silver cyaaaje (See. Smith, J. et al, J- Org, Chem, 1965, 30, 1260-1262).

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Rx, and Ry are any monovalent organic radicals; M is a metal ion; x is 1-4

Scheme 7

10 Suitable bases and solvents are same as defined above.

Metfaodfsl of m^kinttN-OXvcaib@ivicafb-nngte and N-oxycatbo nvlufea_linkages:

The N-oxycarbonykaibaniate (or N-oxycaïbonylttrea) linkage between, the linker and drug cm, be made as shown in Scfeeme S. Thus, catbannate nitrogen can be acylated "by suitable for π nyl cMo $\dot{\eta}$ d β derivatives such as alfcylojcyoarbonyl chloride;,

irgidazolide and the like, to yield the corresponding N-alkyloxycarbo fylcarbainate as Alternatively, the N-xycarbonyl«ttb3 mare (or scheme. shown in the oxycarbonylurea) linkage between the ljtøiker and drag can be made by the reaction of an alcohol (or an amine) with carbamoyl isocyanate (IP15A), which caαbe prepared by Icnowti methods such by treatment of carbamate with oxalyl chloride (See, Grefea JL, et al., Syndesis,, 1988, 922-994) or by treatment of a formyl chloride with silver cyanate (See, Kim, n.K. et al., J. Heterocyclic Cheitt. 1995, 32, 1625). Alternatively, Noxycarbo Tykarbatnate (or N-oxycarbonyrurea) can be prepared in two steps. Step 1: reaction of an alcohol or phenol with chtaroearbonyl isocyaaate to give N-oxycatbonyl carbamoyl chloride intermediate (IPiSB) 4 Step 2: reaction of tine it», termediate ÏP15B with the same or anotiier alcohol or phenol or an amine. (For a review on chemistry of chlorocarbottyl isocyauate, sec, Gorbate Tko. V. I. Tetrahedron, 1993, 49, 3227),

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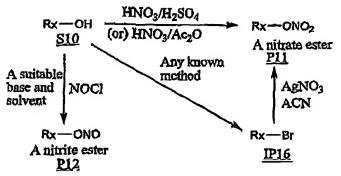
Rx, Ry and Rz are any monovalent organic radicals.

Scheme 8

Suitable bases and solvents are same as defined above.

15 Methodfs> of making Nitrate fnitrooxy) qyyfitcite fmtrosy-oxV) estgr&i

The nitrate or pittite esters can be made as showa 5a Scheme 9. Thus, a nitrate or nitrite estej: can be made py treating an alcotø Λ witii HNO $_3$ /H2SO4 (or HNOa/AcOO) or nitxosyl chloiide, respectively. Alternatively, a nitrate ester can be made by treating a halide (bromide or iodide is preferred) with silver $\dot{\omega}$ ttate in, a polar aprøtic solveint such as acetømtriie.



Rx is any monovalent organic redical.

<u>Scheme 9</u>

Compounds (Prodrugs) of the formula Q containing bio-cleavable lmkere and linkages can be synthesized by various methods obvious to those skilled in the art. As a matter of illustration, any of the approaches shown in the following schemes can be used to make such prodrugs of the fojcrouja (Q described herein.

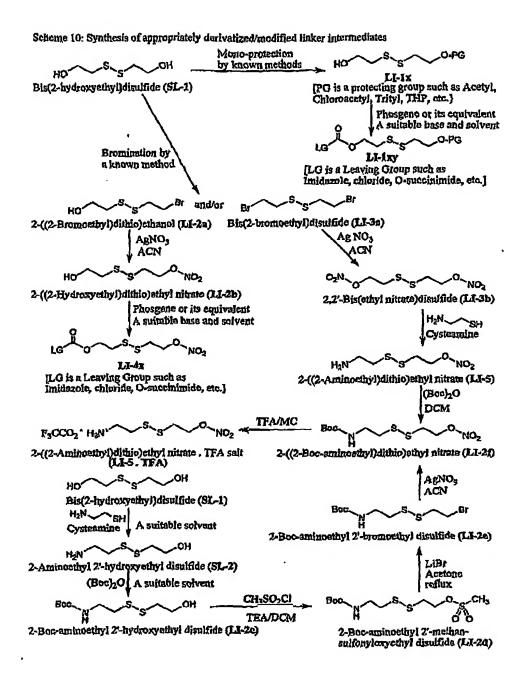
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Monopiotection of dfol ot amjnoaicohol or dianties compounds [i.e., lraker(s)] with suitable protecting groups and their selective removal at appropriate stage of £he syttfhesis are earned out as described in, Theodora W. Greene and Peter O.M. Wute, "Protective Groups in Organic SyirtHegis", 3rd edition, John Wiley and Sons, inc. New York (1999), the disclosures of which are incotporated Jiereia by reference. Suitable protecting groups (PGs) include, but ate not limited to, acetyl, Bcc, Fmoc^ benzoyl, pivAloyl, trityl, teteahy4ropyiacrtyl (THP), and silyl (IBDMS, XMS₅ etc.). Obviously, selection of a suitable protecting group is very crucial for the success of a chosen method for the synthesis of prodrugs described in Hús invention.

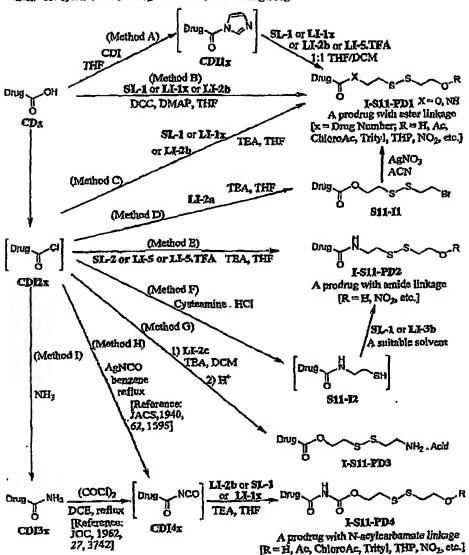
Synthesis of appropriately deiivatized/tnodiEed bM>Jabile linker is shown in Schema 10.



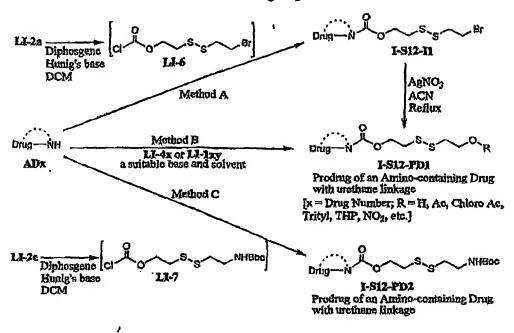
Some of the methods for the synthesis of prodrugs (including NO-releasing prodrugs) of carboxyl-, amino-, and hydroxyl-containing drugs are shown in Schemes 11 through 14.

Scheme 11: Synthesis of Prodrugs of Carboxyl-containing Drugs

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Scheme 12: Synthesis of Prodrugs of Amino-containing Drugs



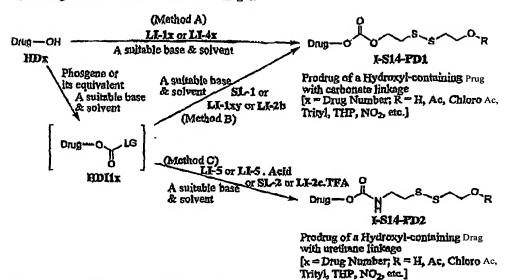
Scheme 13: Synthesis of Prodrugs of Amide/Sulfonamide-containing Drugs:

Prodrug of an Amide/Sulfonamide-containing Drug with N-oxycarbonylamide/sulfonamide linkage

AMDx is a $CONH_Z$ -containing drugs such as vapromide, levotiracetam, carbamazepine, and the like. SAMDx is a SO_2NH_Z -containing drugs such as valdecoxib, celecoxib, and the like.

Scheme 14: Synthesis of Prodrugs of Hydroxyl-containing Drugs

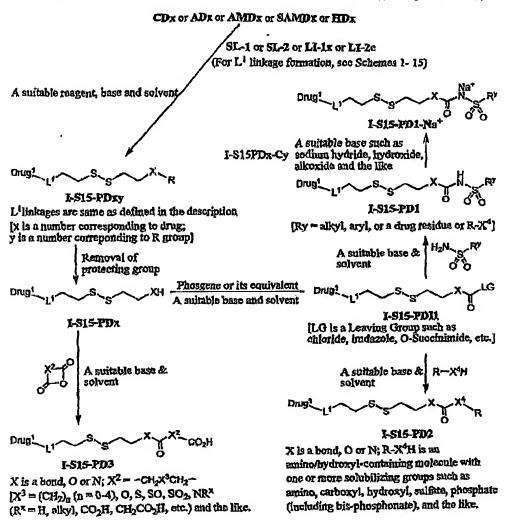
A) Prodrugs with carbonate and carbamate linkages:



B) Prodnigs with N-oxycarbonylcarbamate linkage:

Some of the methods for the synthesis of prodrugs (including NO-teleasing prodrugs and water-sohble prodtugs) are slnowed in Schemes 15 and 16.

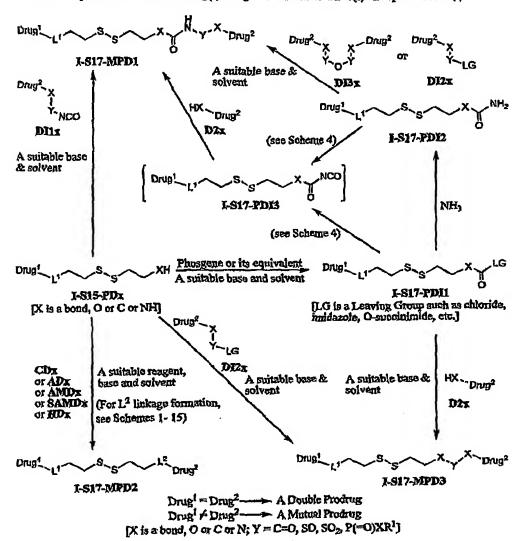
Scheme 15: Synthesis of Water-soluble Prodrug(s) using a bio-cleavable linker(s) and spacer linker (s)



Scheme 16: Synthesis of Prodrugs containing a biocleavable linker and various types linkages

Double/Mutual prodrugs described in this invention can be synthesized by any of the approaches depicted in Schemes 17 through 19.

Scheme 17: Synthesis of Mutual Prodrug(s) using a bio-cleavable linker(s) and spacer linker (s)



Scheme 18: Synthesis of Double/Mutual Prodrug(s) with additional linkers

Scheme 19: Synthesis of Mutual Prodrug(s) using modified bin-cleavable linker(s)

Scheme 20: Synthesis of Mutual Prodrug(s) using modified bio-cleavable linker(s)

As a matter of illustration, mutual prodrug of deslorated and pseudoepfaid π ne m s synthesized as depicted in Scheme 21.

Scheme 21: A Mutual Prodrug of Desloratadine and Pseudosphedrine

Scheme 23: Generation of Paclitaxel from a Prodrug of Isotaxel

Y = O, NR^1 ($R^1 = H$, Aikyl, Aralkyl, Cycloalkyl), (CH_2)_nC(=0) (n=1-6), (CH_2)_n CO_2^- Z = C=0, SO_2 , $P(=0)YR^3$ ($R^3 = H$ or a metal ion)

 $R^2 = H$, a bond, $CH_2CH_2N(CH_3)_2$. HCl, an Amino acid, or any molecule containing solubilizing groups such as carboxylic acid, sulphonic acid, hydroxyl, amino groups, polyethyleneglycol (PEG), a metal ion such a Na⁺, Ca $^{2+}$, etc.

Scheme 24: An alternative method for the synthesis of Linker Intermediates LI-2b and US

Example 1

Synthesis of 2-[(2-hyotroxyethyl)ditiiio]ethyl acetate (LI-la):

Acetic anhydride (5.67 mJ, 56.87 mmol) and pyridine (40,4 ml, 499 wmol) were added to a solution of 2- ϕ ydro χ ye%l)disulfide (SL-1, 15.39 g, 99.78 ira π ol) in DCM (350 mL) at RT and the mixture was stifled at RT for 16 h. The mixtwe was concentrated and the residue, after usual aqueous work-up -aid ckomatographfc purification, afforded \$.16 g (42%) of LI-la α s a pale yellow oil. ¹H-NMR (300 MHz, CDCfe): δ 2,00 (bs, IH), 2.08(s, 3H), 2.80-2.95 (m, 4H), 3.89 (t, 2H, J = 6 Hz), 4.35 (t, 2H, J $^{\circ}$ 6 Ha), MS: (m/z) 219 [Mf.

Example 2

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Synthesis of 2-{t2<t^ahydro'2H-pyraQ-2-yloxjr)et Σ yl3dithio}efii_inol (LI-Ib); This compound was synthesized by a method described by K. R Bemady *et al.* Org. Chem., 1979, 44, 1438. Dihydropyran (S.41 g, 100 iwsnol) was added to a solution of SL-1 (15.4 g, 100 π wnol) in DCM (200 mL) at 0-5 "C, followed by PT8A (-5%) and stilted at RT for 5 h. The mixture, after usual aqueous work-tip and chromatographic purification, adEforded 14.5 g (50%) of LMTb. ¹H-NMR (300 MHz, CDCi₃): B 1.5-1.9 (m, 6H), 2.88 (t, 2H, J = 6 Hz), 2.94 (t, 2H, J = 6 Hz), 3.45-3.57 (m, IH), 3.57-3.78 (m₅IH), 3,85-4.05 (m, 2H)₅3.90 (t, 2H, J = 6 Hz), 4.65 (s, IH).

20 Example 3

Synthesis tsf2-{[2-(Twtyloxy)c%l]dithio}ethaaol (U-Ie):

This compound was synthesized by a method described by O. Hernandez *et al* > *Tetrahedron Letters*, **1981**, 22, 149M494. Thus, 8.58 g (21.4 mmol) of 4-dimethylamino*N-triphenylt β hylpyridi π ium chloride (A.V. Bhatfa et at, *Organic Synthesis*, **1997**, ZJ, 184-185) was added to a solution of **SL-I** (3.0 g, 19.45 mraol) m DCM (90 wL) and strøed at RT for 24 h. The mixture, after usual aqweG work-up and chromatographic purification, afforded 2.86 g (37%) of **LI-Ic.** 1 H-NMR (300 MHz, CDCl $_{3}$): 6 2.70 (t, 2ft J = 6.0 Hz), 2,88 (t, 2H, J - 6 0 1 Hz), 3.39 (t, 2H, Jr - 6.0 Ife), 3.80 (q $_{5}$ 2H, J = 6.0 Hz), 7.24-7.33 (m, JOH). 7.44-7.46 (m, 5H). MS (m/z): 396 IM] $^{+}$.

Example 4

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- Synthesis of chloroacetic acid 2-(2-hy Λ₀ χyβthyldisulfanyl)ethyl ester (LI-Id):

 To a solution of SL-I (23 g, 150 xranol) in DCM (250 mL) at 0 °C were added TEA

 (10.12 g, 100 π_{wc}Col) and chloroacetyl chloride (11,3 g_w 100 mmol) and stirred overnight at RT. The reaction mixture was concentrated and purified by column chromatography to affbrit 8.3 g (37%) of LI-W. ¹H-NMR (300 MHz₃ CDCl₃); 0 2.88 (t, 2H, J « 5.7 Hz),
- 15 2.95 (t, 2H, J 6,6 Hz), 3,89 (t, 2H, J $^{\circ}$ 5.7 Hz), 4.05» (s, 2H), 4.47 (t, 2H, J = 6.6 Hz), Example 5

Synthesis of 2-((2-hydtoxyethyl)dithio)ethyl nitrate (LI-2b) and 2,2'-bis(ethyl nitrat β)di3u!fide (LI- θ b):

These intermediates were synthesized b two steps as sho-w π in Scheme 10.

- Step 1: Synthesis of 2-((2-brojmoei.ayl)dithio)e1banoï < JLI-2\(\hat{I}\) and bis(2-btojaoeithyl)disulfide (LI-3a): These compounds can be syntøestøseti via brøminati On of SL-I by a known bromination methodl, (For a suitable bromination method, see Eruniss, B.S. & al., Vogal's Text Book of Practical Organic Oiotoistty, 5th edition, Pearøon Education, Singapore, 1989; pp 559-579). The following niefhoda were explored:
- Method 1; To a solution of SL-I (ISg, 97.4 πunol) in DMP (50 mL) was added PPh₃ (25.5g, 97.4 tamol) m d cooled to 0 °C, Bromine (3.33 τη/_j 649 ftunol) was added dropwise and stirred at RT for 18 h. ILC of the mixture showed Ac mono-br Graø derivative LI-2a as the major product with only trace amounts of dibiomide LI--ta The mixture was diluted -with water and extracted with BtOAc. A βcr usual aqueows -woric-np and chiom_f tographic purification 3.65 g (26%) of U-2a were obt&ined. ¹H-NMR (300 MHz,

CDCl₃): 6 1.82 (s, IH), 2.88 (t, 2H, J = 5.8 HB), 3.08 (t, 2H, J = 7,90 M), 3.63 (t, 2H, J * 7,90 Hz), 3,90 (t, 2H, $J \times 5.8 \text{ Ez}$).

Methp.d2; To a solution of SIrI (40 g, 0.26 mol) j& DCM (400 mL) at 0 °C was added a solution of PBr₃ (24.62 mU 0.26 mol) in DCM (50 mL) and two mixture was suited at RT for 15 k TLC indicated formation, of LI-3a as the major product with trace amounts of LI-2ft. The reaction was quenched by Hie addition of water and extracted with DCM, After usual aqueous worfc-up and chromatographic purification, 33 g (45.3%) of LI-Sa were obtained. ¹H-NMR (500 UBz, CDCI₃): 6 3-1-3.15 (m, 4H), 3.60-3.66 (m, 4H). MS (CI)⁺ m&; 277.69 {M+HJ*, 279.66. A Qalternative synthesis of LI-3s has been reported.

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MsffiQ<L3: To a cold suspension of SM (20 g, 129 romol) in PCM (400 xnL) was added CBr₄ (42 g_> 129 mmo i) sad stitted for 10 jniα pphs (34 g, 129 mmol) wa\$ then added and stijted at RT fot 14 h₂. The tcacion mixture was concentrated and the residue purified by caiman cfroHistography to give 13.5 g (52.3%) of LI-2a and 13.0 g (36%) of LI-Sa.

(Sharma, M. et Ol, Bioorg. Med Chem. Lm, 2004, 14, 5347-5350),

15 These compounds were identical (by TLC, NMR and MS) to thbs β obta ὑtød in Methods 2 and 2 described above.

Synthesis of 2-((2-hydroxy6lihyil)dith_o)ethyl titrate QJi-Zb): To a solution of Lï-2a (2g, 9.21 nimol) in acetonitrile (IS mL) was added AgN θ_3 (I.SSg., 11.05 xmnoï) portion-wse and the mixture was stirred at RT in the dark for 45 min. The reaction mixture was filtered through ccüe artd the filtrate was concentrated. The residue^ after usual aqueous work-up and chromatographic pwificaiioa g»ve ï.46 g (74%) crude UrZb -which was used for the next reactioE without further pwific^ ion. A Λ analytical sample voas obtained by chromatographic purification. 1 H^NMR 000 MHz, CDCI?): S 2.89 (t, 2H, J - 6.0 Hz), 2.98 (t, 2H, J * 7.5 Hz) $_9$ 3.90 (t, 2H, J « 6.0 Hz), 4.74 (t» 2H, J - 7-5 Hz); MS (EI)⁺ (m/2): W [M]".

Synthesis of 2,2'-bis(ethyI nitrate)di Euifide *QLI-3b*): AgNC[^] (8,01 & 47. J2 mrool) was added portion-wise to a solution of LI-3& (6.0 g»21.42 mmol) in aoetoj $\dot{\omega}$ rite (40 ∞ L) at RT in the dark and stiired for 30 win. The mixture was filtered through cellite and the filtrate was concentrated *in vocato* at 35 $\dot{\omega}$ C to aSbrd 4.6 g (β S%) of Li-3b, which was used without farther purification. An analytical sample vw obtained by chromatograpMc

purification (3-15% BtOAc in petroleum ether). 1 H-NMR (300 *MHz*, CDCJ₃): δ 3.10 (t, 4H, J - 6JH $_{s}$) $_{f}$ 4Jl (t $_{J}$ 4H,J-6JH2). MS (EI) $^{+}$ m/z: 244 (M] $^{+}$. Example 6

Synthesis of tert-bufyl H &-hyh m yethyl) ditbio]ekylcai bm se (U-2c); To a solution of cysteami π e hydrochloride (15 g, 132 mntøi) σ MeOH (130 xnL) at 0-5 σ C was added TEA (37 mL, 264 mnol). Mowed by a solution of SL-I (20,4 g, 132 rømol) in PCM (50 mL) and stirred at RT for σ h. The mixture, -which confined the intermediate SL-2, was cooled and (Boc)₂O (63.4 g, 290,4 tnmol) was added and stilted overnight, McOH was removed uOdsr vacuum. After usual aqueous wofk-up and chromatographic purification, W-2c was obtained as a colorless oil (14,6 g, 44%).

The above Baker intermediate can also be prepared by th& following method; Step 1: TEA (37 røj, 264 cm cii) and a solution of $(Boc)_2O$ (48 g, 220 mi π ol) in DCM (100 xnL) were added to a suspension of cysteine ^hydrochloride (20 g, 88.8 m π iol) in of DCM (300 mh) m d stirred at RT for 15 h. The whether was concentrated and the residue after visual aqueous worfc-up and cfiroi π atographtic purificadoa, gave 30 g (96%) of tert-butyl 2<{2-[(t^-butoxy<^tbo cyl)a β Mtto]e%l}dilMo)t*hylcarbaroate as a white solid. 1 H-NMR (300 MHz, CDCl₃): δ L43 (s, ISH), 2.78 (t, 4H, J = 6.3Hx)₃ 3.44 (q, 4H, J = 6.0 Hz), 5.00 (bs, IH). MS (m/z): 353. IS [M+Hf, 375.24 (MfNa]*.

Step 2: A solution of 2-mercapto β t.ianol (1.44 g, 18.5 ramol) in DCM (10 mL) was added to a *nuxme* of teit-butyl 2-({24(^-b«toxyc^onyl)amino3e(liyi}diMo)elhyl catbamate (5.0 g, H.2 xiiod) and TEA (3,87 ml, 27J π iraoi) in DCM (30 mL) and stirred overnight at RT. Aftw usual aqueous workup and chromatographic purification, 2.0 g (56%) of M-2c was obtained. ¹H-NMR (300]MHz, CDCl₃): δ 1.43 (s, 9H), 2.79 (t, 2H₅J = 6.5Ha), 2.87 (t, 2H, J = 5.7Hz), 3.48 (q, 2H» J - 6Hz X 3.S8 (t, 2H, J = 5.5 Hz), 4.S (bs,lH). MS (i π z): 254 [M+Hf 5276.13 [M+Naf,

Removal of the Boc group of W-2c was accomplished as described in Example 10 to afford Uje TFA salt, LI-2c.TFA.

Obviously, the linker intenaediates W-2b and U-2c can also be syttfhestøsd by following the method outlined in Scheme 24.

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Example 7

Synthesis of 2-Boc*dtinoethyl~2"metimsulfonyloxy&Ihyl disulfide (LKW): To an ice-cold solution of LI-2c (9 g, 35.52 mmol) fi DCM (80 mh) and TEA (9,9 mL, 7L04 røraol) was added jijethsnesulfonyl chloride (4.2 mL, 53.28 mmo]> the reaction mixtrøe was stirred at 0-5 °C for 45 rain, then diluted with DCM, After usual aqueous work-up and chromatograpitic purification, 13.38 g of LI-2d were obtained, which was pure eπougfr for fattier use. H-NMR &00 MHz, CDCl₃): δ 2.43 & 9ti), 2,80 (t, 2H, J * 6.4 Hz), 2.98 (1, 2H, 5.7 Hz), 3.05 (s, 3H), 3.35-3.45 (m, 2H), 4.45 (t, 2H, J « 6.7 Hz), 478 \$>rs, IH).

10 Example S

Synthesis of 2-Boc~aminoe%t-2'%omo&thyl disulfide (LI-2 β)t To a solution of U-2d (13 & 39.57 mtnol) in acetone (100 mL) at RT was added LiBf (6,82 g, 78.54 mml) and stiired under reflux for 1 6. The reaction mixture was concentrated and the residue, after usual aqueous wodc-up and chromatographic purification, afforded 8.8 g (78%) of LI-2e.

¹⁵ H-NMR (300 3MHz, CDCl₃); S 144 (s. 9H), 2.80 (£, 2H, J = 6.32 Hz), 3.06 (t, 2H, J \ll 6,73 Hz), 3.44 (q, 2H)» 3.61 (t, 2H, J = 7.62 Hz), 4,87 (br s, IH). MS (EI)⁺ m/z: 317 mm +-

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Synthesis of 2<(2-Boc-ao $\dot{\omega}$ ioethyl)aiftiio)ctihyl nitrate (LI~2f): To a solution of XJWe (8 g, 25.3 mmoJ) in acctowif-^e (80 nOL) was added AgNOj (5.16 g_? 30.36 mmol) pottio Λ wise and stilted at RT for 1 it in the desk. The mixture was filtered flirøu\$ t ccHte and the filtrate was concentrated. The residue obtained was purified by column chromatography of affoKl 6.34 jg(S4%) of U-2f. ¹H-MMR (300 MH*, CDCl₃); δ 1.44 (S₅9H)₄2.80 (tw2H, J = 6.32 Hz), 3.06 (t, 2H, J * 6.73 H Σ , 3.44 (q, 2H), 4.70 (t, 2H, J - 7.62 ETs)₃ 4.87 (br s, IH). MS (ElpWz: 299 ptf+Hf.

The above Miife'r intermediaie was also prepared by the foJJow@g method: TEA (3.56 g, 35.2 π unol) was added to a solution of cystea $\dot{\omega}$ ine hydrochloride (2g, 17.60 mrøol) and U-3b (4.29g, 17.6r@nol) in methanol (25mL) at 0 °C and stiired at RT tot 4 $\dot{\omega}$. To the mixture' which ootitajned $\dot{\omega}$ e fate π nediate j $\dot{\omega}$ e amine (LI'5)» a solution of (Boc>0 (7,68 g, 35.2 nraiol) and TEA (3.56 & 3S.2 niflaol) in MeOH (IQmL) was added and the inixfcure was stirred overnight. The j $\dot{\omega}$ ectiow raktws was filtered through celite

and evaj^j orated to dryness. The residue was purified by column chromatography to afford 0.380g(7 %) of U-2f.

Example 10

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Synthesis of 2-((2~Aminoe%,)dithio)e1Ii.yl nitrate.TFA salt (LI-5/IFA); To an ice-cold solution of *LUt* (2 g, 6,7 rnmol) in DCM (20 mL) was added TFA (5 ml) and stiwed at room temperature for 1 h. The mixture was concentrated, the residue was triturated with ether and conciliated to jtsrøove traces of TFA and finally dried to afford *UrS-WA*, which -was used as such m further reactions.

The above linker intermediate M-SJTFA was also synthesized as described bekw TEA (3,56 g, 35.20w tol) was added drop-wise to a solution of cysteanoine hydrochloride (2g, 17.60n.mol) and LI-3b (4.29g, 17.6mmol) in MeOH (25mL) at 0 °C and stirred at RT for 4 Jh. The mixture was cooled to 0 °C and a solution of (Boc) 2O (7,68 g, 35.2tnmol) in MeOE (10 mL) was added, followed by TEA {3.56 g, 35.2mmø!}, and stfrred overnight at RT. The reaction mature vms filtered through celit β and the filtrate concentrated. The residue was purified by coltrø α chromatography to afford 0,38 g (7.25%) of Urøf, which was identical (TLC and ¹H-N VfR) to that obtained in Example 9. Removal of the Boc group from LI-2f to give LI-5.TFA was accomplished as described in Example 10.

Example II

Synthesis of πtethyl f(2-hvdroxvethyndtthio1ac&tate (LSIIa): Methyl mβrcaptoacetate (10.32 g, 97-4 mmol) ^as added b a solution of Sir* (10.0 g, 64.93 mmol) in DCM (150 røL) at RT, followed by TEA (18 rnL, 129 mmol) and the mixture was stated ov βtnight at RT, After usual aqueous work-iφ and chromatographic purification, 2.7 g (22.9 %) of L3ï2a were obtained. H-NMR (300 UHz₇ CDCl₃: δ Z95 (t, 2H, J » 2.5 Hz), 3.49 (s, 2H)₃ 3.76 (s, 3H), 3,86 (q, 2H, ï * 5.64). MS (tn/2): IiZ [M+H] +.

Example 12

Synthesis of prpdmg 1..CI-PDIO: This prodrug was synthesized as described in Scheme 11, Method B. Thus, TEA (0.75 mL, 10 mmol) -was added to a svispension of cetirizine dihydrochlorid θ (2.0 g, 4,68 mmol) in DOM (50 mL), followed by a solution of SL-I (0.72 g, 4.67 uwnol). DCC (1 Λ 3 g, 5,47 mmol) and DMAP (0.1 t2g» 1 mmol) and stirred at RT for 15 h. The tnixiwe vrøs concentrated and the residue, after \isVial aq.v»eora work-

up and chromatographic pudfication, gave 0.44 g (19%) of I-Cl-PDIO. ^IH-NMR (300 MHz, CDCl₃); S 2 J O (bs, 4H), 2.SQ (bs, 6H), 2,87 (t, 2H, J * 6.09 Hz), 2.94 (t, 2B, J * 7.32 Hs), 3.75 (m, 2H), 3,86 (t,2H, J = 6.12 Hz), 4.B (S, 2H), 4.24 (s, IH), 4.40 (f, 2H, J = 5.09 Hz) aijd 7.22-7.35 (m, 9B). MS (∞ /z): 527 [M+H]⁺.

5 Example 13

Synthesis of Prodruß I-C1-PD6: Step 1: To a suspension of aspirin (3 g, 16.65 HUM_OI) in benzene (25 ml) and DMF (2 drops) at 0-5 0 C was added oxally chloride (1.7 roL, 19.98 mmol) in benzene (5 mL). The reaction π jixhire was refluxed at 85 0 C foi 2 h, cooled to RT acid concentrated to give a yellow oil.

- Steφ 2: The yeiiow oil was dissolved in benzene (30 mL), silver cyanate (2.99 g, 19.98 üwnol) was added and the mixture was tefluxed foi 1_{jhi} in the daifc
 Step 3; Hie reaction mixture was cooled to RT, and a solution of SIrI (2.56 g, 16.65 ttimol) in benzene (5 xnL) was added. The reaction mixture wag stored for Zh, filtered through celite, concentrated and purified by colraan chromatography b afford 2.24 g (54%) ofl-CI-PZWf. H NMR (CDCI₅, 300 UHz): B 2.12 (s, 3H), 2,83-291 (m, 4H)₇ 3,84 (t, J « 5,9 Hz, 2H), 4.27 (t, J 5.16 Hz, 2H)_>6.20 (fjr s, IH), 7.06 (d, J = 8.21 Hz, IH), 7.19 (t, J = 735 Hz_> 1J9), 7.59 (^ J 7.24 Hz, IH); 7.97 (d, J = 6.82 Hz₃ IH)- MS; m/z 360.06 [M+Hf , 377.05 [M+^?[i]t]⁴, 38^0.01 fM+Naf , 357.9\$ IM-HJ'. Example 14
- 20 Synthesis of j tfodbug X-CI-PDIItTo a soMon of SL-I (7g, 45.45 mmol) and valproic acid (7.8S g, 54.5 mmot) ia DCM (80 mL) was added DCC (11,26 g, 54,5 πjunøl), followed by DMAP (6.65 g, 54.5 mmol), anil ωe resulting is Tispension was stiired at RT for 18 it. After usas ü aqueous vwäk-υp and Chromatographic proification, 2.82 g (22 %) of J-CX-PDII we we obtained as a colorless oil. H KMR (CD<-% 300 MHz); δ 0.86-0.93

 25 (m, 6H), 1.22-1.29 (m₃ 8H), 1.32-1.59 (m,4H)₂ 2.37 (m,1H0, 3.S? < 2H, J = 5.7 Ha),

Example 15

4J5(t ₃ 2H, J~ 6.5Hz).

Synthesis of prodrug 1-C1-PD13: To a solution of vatyromide (5 g, 34.9 mmol) in DCB (50 ittL) w s added oxalyl chloride (3.7 itttL, 41.8S $mm\dot{o}i$) at 0 0 C and tefluxed far U h.

30 The jnixUire Nvas added to a solution of SL-I (10.76 g, 69J8 mmol) ia DCE (SO mL) and stated overnight at RT. After iisusl aqueous work-up and chromatographic purification,

5,01 g (44%) of I-C1-WM3 weie obtained as a colorless oil. ³H NMR (CDCl $_3$, 300 MHz); S 0.89 (t, 6H, J $^{\circ}$ 7,21 Hz), 1.23-1.66 (m, 9H), 2.90 (t, 2H, 5.82 Hz), 2.97 (t, 2H $_5$ J= 6-46Hz), 3.90 (t, 2H, J=* 5.82Kz), 4.44 (i, 2H, J= 6.48 Hz), 7, 61 (br s, IH) Example 16

Synthesis of prodrug I-C1-PP14; To a cold solution of diphosgene (0.9 mL, 7.14 nunol) in DCM (5 mL) was added a solution of Ï-C1-PDU (1 g₃ 3.57 tnmol) and DIPEA (1.9 mL, 10,71 mmol) in DCM (5 mL). The reaction mixture was stiffed at RT for 30 mitt. DCM and excess phosgene were removed under vacuum and the resulting solid was dissolved in DCM (5 mL), To it "was added a suspension of mβhaiiesulfona πide (0.41 g, 4.284 mmol) and DIPEA (1.9 mL, 10,71 rønol) in DCM (5 mL) at 0-5 °C and the mixture was stored overnight at RT. After usual aqueous work-up and chromatographic purification, 1.1 g(77%)of ï-Cl-røl4w εredbtainedaaawWt βsolid. ¹HNMR(CDCl 3, 300 MHz): δ0.89 (t, 6H, J * 7.22 Hz), L27-1.63 (m, Stl), 2,34-2.4\$ (m, IH), 2.90 (t, 2H_a J = 7,0 Hz), 2.% (t, 2H₅ J - 643 Hz), 3.30 (s, 3H), 4.36 (t₂ 2H₂ J * 6.99 Ez), 4.45 (t, 2H, J - 6.14 Hz). MS: (BS") ro/z 402 tM+H]+, 419 [M+NK,f , 424 [M+Na]+, 440 (M+Kf; (ES-) 401 [M-Hj;

Esawiple 17

Example 18

Synthesis of prodrug I-A1-HM;

This prodrug was synthesized as shown in Scheme 2. Thus, to a solution of amtodiptae (18,75 g, 45.86 mmol) in DCM (100 mL) at 0 0 C was added triphosgene (4.62 g_> 15.59 π røol) followed by TEA (7.71 g, 7635 maiol) in DCM (10 mL) and sŵred at RT for 3 h. To tibi« was added a solution of Lt-U (9.0 g, 48.86 mmol) and TEA (4.63 g, 45.86 eunol) in DCM (10 mL) at 0 0 C and statied at RT for 3 d. *The* mixture vras concemtrated and we residue jpurified tyy column chromatography to yield 23 g (79.5%) of K-Al-PDl tø-÷NMfc (300 MHz_>CDCls): δ M 6 (t_s 3H, J - 7.5 Hz), 2.05 (s, 3H), Z34 (s, 3H), 2.86-2.94 (in, 4H), 3.43-3.45 (m, 2H), 3.59-3,62 (m, 5H), 4.0-4.35 (m» 4H), 4.30-4,35 (m, 4H), 4:69 (q, 2H, J « 15 Hz), 5.20 (b\$, 1H), 5.38 (s, 1H), 7.01-7.34 (Kt₇ 4H). MS (m/z): 631 [M+Hf , 653 [M+Naf .

30 Synthesis of prodrug I-A1-PD2: To a solution of I-Al-PDI (23.0 g, 36.45 mmol) ja MeOH (250 mL) at 0 $^{\circ}$ C was adaed a solution OfK $_{2}$ CO $_{3}$ (7.54 g, 54.67 mmol) in water

(55 mL) and stirred for 10 tain. The mixture was concentrated and purified by column chromatography to afford J8 g (83.8%) of the prodrug X-Al-PDZ ¹H-NMR (300 MHz, CIDCl₃): δ I.I* (U 3H, J = 6 Hz), 2.35 (s, 3H), 2.84-2.88 (t, 2H, J « 6 Hz), 2.90-2.94 (t, 2H, J - 6 HzX 3.44 (bs, 2H), 3.59-3.61 (bs, SH)₉ 3.84-3.91 (m, 2H), 4,0-4.03 & 2H, J = 3.11 Hz), 4.33 (bs, 2H)₄ 4.69 (q, 2H, J = 15 Hz), 5.28 (bs, IH). 5.37 (s, IH), 7.32-7.36 (m,4H), MS CES^ro/z 589 [M⁺J-611 (M+Naf.

Example 1J>

Synthesis of prodrug I-Al-P»3:To a suspension of laraotrigine (13.09 g, 51,02 mmol) in toluene (100 mL) at U O 0 C was added a solution of W-lxy (sj 0 Unesized from tl- $^{\circ}$ I a and CDJ, as described in Scheme 10) (16,27 g, 56-12 mmol) in THF (50 JOTL) acid stirred at 110 0 C overnight The reaction mixtate was purified by column chromatography to give 6,0 g (24%) of X-Al-PD3 as a white solid. 1 H NMR(CXJ $_5$ OD, 300 MHz) δ 2,04, (s, 3H), 2.96-3.02 (m $_{\rm w}$ 4H), 430-4.35 (m, 2H), 4.45 (t, 2H), 7.38-7.45 (tn, 2H), 7.67-7,69 (m, IH). MS: (ES $^+$)lnZs $_{\rm w}$ 477,9 (MH-H) $^+$, 499.9 (M +Na)*.

15 Example 20

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Example 21

Synthesis of prodmg IA I-1PD5Ï To a solution of diphosgen β (0.99 ntl[^] 8.24 mmol) in PCM (3 mL) at 0 °C was added a solution of L3Ka (0.5 g, 2.74 or oo]) and Hüπig's base (2.39 mL, 13.73 KHΠοΪ) in DCM (3 mL). The jtmxtroe vvas stirred at 0 °C for 30 rain and concentrated to yield the njtcroicdiate JLSBa as alight-yellow semi-solid. A solution of a mixture of gabapeatin ethyl ester hydrochloride (0.77g, 329 mmol) and Hfinig's base (1.7 niL, 9.79 mmd Ï) TA DCM (6 mL) was added to the intermediate JJSB* at RT and stilted foi 15 h. After usual aqueous work-up and chromatographic purification, 0.34 g (30 %) of I-A1 "PI>S were obtained as a yelbw oil. H MMR [CDQh, 300 MHz): δ 1.26

(t, 3H» J = 6 He), 1.22-1.51 (m, 10 H), 2.26 ($\$_s$ 2H), 2.96 (t, 2H₉ J- 6 Hz), 3.1S (d_>2H, J= 6 ft.), 3.49 (s, 2H)₃ 3.82 (s, 3H), 4.09 (q, 2H, J- 6 Hz), 4.29 (t, 2EJ ^ 6 Hz), 5.39 (bs IH). MS: (ES") m/z 408 (M+H)+, 430 (M+Naf; (ES^ m/z 405 (M-H)'. Example 22

- Synthesis of prodrtig I-AlrPDti: To a solution of I-Al-PIrø (LO g, 2.63 mmol) in DCM (3 rat) at RT was added CDI (0.46 g, 2.89 mmol) and stirred for 15 k A suspension of serine methyl ester hydrochloride (0.61 g, 3.95 mmol) in DCM (4 mL) and TEA (1.1 mL, 7.90 mmol) was added and stirring continued for 15 h. After usual aqueous work-up and chromatographic purification, 0.706 g (51%) of I-A1-FD6 were obtained as a colorless oil. H NMR (CDCl₃₁ 300 MHz): δ 1,25 (t, 3H, J «·7,1 Hz), 1.35-1.51 (m, 10H), 2.28(s_> 2H), 2.91-2.98 (m_s 4H)₅ 3.16 (fi, 2H, J = 9Hz), 3.78 <s, 3H), 3,94-438 (m, 9H), 5.5 (bs_w IH), 6.0 (bs, 1H[). MS: (ES)+: m/z S25 (M+H)*, 547 (M+Na)+. (ES)"; m/z 523 (M-H)+. Example 23
- Synthesis of prodrug I-Al-fD?! TO a soïutuion of Ï-Al-PD8 0 6 mg, 0-22 πunol) in DCM (9 mL) at RT was added CDI (40 mg, 0.24 mraol) and stirred for 15 h, afler which a solution of dimetihyl glutemate (SO mg, 0,45 mmol) and TEA (0.06 mL, 0.45 mmol) was added and stiir Ed for 2 d. After usual aqueous work-up and chromatographic purification, 97 mg (74 %) of Ï-Al-3PB7 were obtained as a colourless oil. H NMR (CDCl₃, 300 MHz): S 1-25 (t, 3H_> J=7.I3 Bz), 1.36-2.5 (ro, 16H)₇ 2.93(X₇ 4H, J = 6.46 Hz), 3.19 (d, 2H, J 6.67), 3.67 (s, 3H)₇ 3.74 (s, 3H), 4,12 (q, 2H₇ J « 7.13 Hz), 4.25-4.44 (m, 5% 5,4 (bs, IH)₁ 5.65 (bs, IH)- MSt (ES+) m/z SSI (M+H)*, 603 (M+Naf; (ES*) m/z 571 (M-H)*.

Example 24

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Synthesis of prodrug I-Al-PDJk To a suspension of gabap Ontin (10 g, 58.4 mmo^j) in THF (100 mL) at 0 °C was added IN NaOH (70 πiL), followed by (BOc)₂O. The mixture was stirred at RT for 15 L After ivashiag with diethyl ether (100 mL X 2), the aqueous layer was addtfied with solid KHSO₂i and extracted with EtOAc (100 mL x 2). Organic extracts were washed with faritte (100 iflL), dried over NaaSO4 and ctmcentrated to afford 10.41g (68 %) of boivprotected gabapentitt as a white solid.

A Mixture of boc-protected gabapentin (5-0 g_s 18.45 mmol) and CDI (3.59 g_s 22.14 mmol) in DCM (75 dL) was stored for 15 h The mixture was conceatcated and

dissolved in acctonitrile (50 mL), followed by the addition of 30 % aqueous solution of atontronia (SO VdL) and stirred for 1.5 h at JIT. After usual aqueous work-up, 4.5 g (90 %) of boc-piotected gabapentia-amide were obtained as a white solid.

To a solution of boc-protected gabape Otin-arøide (2.59 g, 9.61 tnmol) in DCM (12 knL) at 0 °C was added solution of IFA (4mL) in DCM (4 mL) and stitred for 2.5 h at RT. The mixture was concentrated and dissolved in DCM (20 ml). This was treated successively wi β i Hunig's base (6.7 π L, 38.46 flunol) and LMa (L45g, 7.39 mmol), and stitted at RT fiw 3 h. After usual aqueous work-up and chromatographic purification, 1.19 g (41 %) of I-Al-Hrø were obtained as a ysliow oil. ¹H NMR (CDCl 3, 300 MUz): δ 1,28-1.4« (m, 10H), 2-06 (s, 3H), 2.15 (3, 2H), 2.91 (t, 4H, J « 6.0 Hz) 3.23 (4, 2H, J = 6.0 Ha), 4.2g-438(jn, 4H) 3.5.7(bs, IH). MS: (ESf m/z 393(M*H)*; ϕ Sy m/s 392(M-H)'.

Example 25

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Synthesis of prodrug 1. Al-PDIO: A mixture of I-AWD8 (1.0g, 2.63 mmol) and CDI (0,469 g, 2-89 mmol) in DMF (3 αL) was stirred for 12 h, after which N^ 'dimethylethylene-Kaπxme (0.56mL 2,5,26 rømol) and DMAP (0.32 g, 2.63 mmol) was added. The mixture was stirred for 4 ln, After usual aqueous woife-tφ and chromatographic purification, 0.763 g (59 %) of I-Al-tDIO were obtained as a yellow oil. *H NMR (CDClj, 300 MHz): δ 1.25 (t, 3H, J = 6.0 Hz), L28-1.53 (m, 10H)_s 2.24 (s, 6H), 2.29 (3, 2*0, 2.42 (t, 2H₁ J » 6,0 Hz), 2.92 (t, 4H, J * 6.0 Hz), 3>20(d>2H, J * 6.0 Hz), 3.26 (q, 4H, J - 6-0 Hz), 4:13 (q, 2H, J - 7,0 Ha), 4.31 (t, 4H, S * 6,0Hz), 7-26 (bs, IH), MS: (ES)+ oris 494 (M+Hf, 516 <M+Na)+; (ES)* nfl/z 492 (M-H)*.

Example 26

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Synthesis of ptodnig I-AX-PIW1: A raixt Oc of IMa (2.0 g, 16,20 aamol) and CDI (L98 g, 12.24 mmol) in DCM (12 mt) was stiinted for 2 h and concentrated. The residue Aas dissolved in acetonitriley and a suspension of gabapentin (2.62 g_f 15.30 mraol) o saturated NaHCO₃ (15 *ml*) was added. The mixture was *suited* at RT for 15 h. Acetonitrile "was removed by cüstiUaβon and ωe basic aqueous portion -was washed with diethyl ether (100 mL x 2). The aqueous layer was acidified using 2K HCl aftd βxtraoted in EtOAc (60 HiL. x 3). The organic layer was concentrated ønd the residue was purified by chromatographic pwification 1.76 g (43 %) of I-ΛH-PDXI were obtained as a

colorless oil. ¹H NMR (CDCt₃, 300 MHz): S 1.27-1.68 (m, 10H), 2.07 (s₃ 3H)₅ 2.31 (s, 2H), 2.92 (% 4H, J - 6.0 Hz), 3.22 (d, 2H₁ J = 9.0 Hz), 4.314.35 \triangleleft m_>4H), 5.43 (bs, IH). MS;(ES) $\stackrel{*}{}$ m/z 392 (M-H) $\stackrel{"}{}$.

Esampl©27

Synthesis of prodrug I-A1-PM3: This prodrug was synthesized as shewn in Scheme 12, Method B. tiros, b a solution of dijihrisgeae (7.02 ÜxL, 58.18 mmol) in DCM (20 JIL) at 0 °C was added a solution of M-Ia (5.71 g, 29.09 mmol) and Hβnig's base (25.3 ml, 145.4S mmol) in DCM (30 mL) and stirred at RT fin- 40 min. The mixture was concentrated and a mixture of gabapentin ethyl ester hydrochloride (7.546 g, 32 mmol) and Htøttg's base (U Λ5 mL, 64 mmol) in PCM (50 xoL) was added and stirred overnight Reaction mixture -was conce πtatcd and, after usual aq Oeoas woii-Mip and coju/ΠιΛ chromatography, 8.42 g (67 %) of I-AMPD13 were obtained. HTSIMR (CDCl 3, 300 MHz): S 1.22 (t, 3H₂J " 7.3 Hz), U7-1.6S (m, 10H), 2.06 (s, 3H)₉2.27 (s_s2H)₇2.91 (t, 4H, J - 6.6 Hz), 3.19 (4 2H, J = 6.7 HzX 4.08 - 4.15 (q₂2H, J * λ J Hz)₇4.27-4.34 (q, 4H, J * 6.4 Hz), 5.4 (bs, IH). MS: rø/z 422 [M+Ei*, 444 UWtrøaf.

Example 28

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Synthesis of prodrug I-Al-FDfc To an ice-cold solution of I-Al-PD13 (S.0 g, 18.98 mmol) Jn MeOH (30 mL) was added a solution of KaCO₇ (5-24 g, 37.96 mmo i) ia water (38 ml). After 15 mto, the mixture was concentrated. After usual aqueous work- Op, 5.0 g (69 %) ofl-Al-PDS were obtained. ¹H MMR (CDCl₃, 300 MHz): δ 1.25 (t, 3H, J = 7.11 Hz), 1.30-1,71 (m, 10H), 2.87-194 (B, 4H), 2.27 (s, 2H), 3.18 (d, 2H, J « 6.6Hz), 3.87 (t, 2H, J * 5.7 Hz). 4,09^.16 (q, 2B, J = 7.12 Hz), 4.31 (t, 2H, J = 6.51 Hx), 5.44 (bs, IH), MS: tn/z 380 ξ M+H3⁺9402 [M+Ka]⁺. K χ ample29

2S Synthesis of porodragI-Al-PB12: To a sotatio α of diphosge πe Q.21 toil-, 15,81 thraol) in DCM (20 mL) at 0 °C was added a solution of Ï-Al-H)8 (4 g, J0.54 mtnoj) and Hunig's base (5-S mt > 31.62 thmol) in DCM (30 ml). The mbttuie was stilted at RT for 40 røfl, cooled to 0-5 °C, and djy ammonia gas was passed through it for 30 Biia Reaction mixture was concentrated a«d, after Tisual aqueous vrork-up, 5,3 g (91 %) of Ï-AUVO ÏZ were obtained, ¹H INMR (CDCl₃, 300 MHz); δ 1.23 (t, 3H, J = 74 Hz), 1.27-1-79 (ro>

10H), 2-2S (s, 2H), 2.91-3.03 (ra, 4H), 3.19 (d, 2H, J, 6.7 Hz), 4.12 (q, 2& J-7.1 Hz), 4.31 (t, 4H» J - 6.4 Hz), 5.4 (t, IH, J = 6.0 Hz). MS; m/2 423 [WKf, 446 [M+Naf. Example 30

Synthesis of prodrug Ï-A1-PD14: Ethyl chlorofojrmate (OM g, 7.9 mmol) was added to a solution of 3-carbamoylroethyl-5-meHiylhexa»olc acid (M. S. HbeJcstra et al, Qrg. Proc. Res. Pev, 1997, U26-38) (1.0 g, 53 mmol) in THF (6 mL) at-10 ⁰C, followed by TEA (2.4 mL, 17.0 mmol) and ttro mixture was stirred at -10 'C for 30 tm. A solution of NaN;? (1.73 g, 26,6 romol) in water (t0 rOL) was added and stirred for 2h at-10 °C. The reaction mixture was brought to RT and extracted with, EtOAc (3 x 25 mL), washed with 10 water (2 χ 25 mL), dried over Na₂SO₄ and concentrated. Toluene (20 mL) was added to the residue and refhrøsd for 6 h. After cooling to RT, a solution, of SL-I (825 tog, 53 Emol) in DCM (10 mL) was added and stirred at RT for 14 K After usual aqueous workup and chromatographic purification, 31S uig (17 %) of I-AJ«PDi4 were obtained as a colorless oil. H NMR (300 MH& CDCl₃): δ0.89-0.9\$ (ra, 6H)₄ 1.25-1.29 (m, 2H)₅ 1.62-1,71 (m_>IH), 2.04-2.1 (no, t H), 2.38 (d_>J * 5.2 Hz, 2H), 2.87-2.95 (ro, 4H), 3.05-3,36 (m, 2H) 13.88 f J *> 5.7 Hz, 2H), 4.34 (t, J " 6.2 Hz₃2H), 5.06 (br s, JH). MS; m/z 338 IMJ*.

Example 31

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Synthesis of jwodrug "-At-PDI \delta Ba: To a solution of I-A1-PD4 (0.350 g, 0.802 mrnol) in DMP (3 mL) at RT was added CPI (0.195g, 1.204 mmol) and stirred at RT for 3 k This mixture was added to ^ suspension of methiaesulphonaniide (0.304 g, 3.2 mmal) in, DMF (4 mL) and NaH (OA53 g₂ 3.2 ramol) at 0 °C and stireed at RT for 4 h. Tb^ reaction was quenched with ice and, after usual aqueous woric-up sod chromatographic putiiflcatioii, 0.12 g (26%) of I-AWDISBa were obtained as a white solid. ³H NMR $(CDCl_3 + CD_3OD, 300MH2)$: $\delta 2.S3 - 2.90$ (m, 4jfJ), 3,10 (s, 3H), 4,264.36 (m, 4H), 7.19-7.28 (m, 2H), 7.48-7.51 (m, IH). MS: (ES *) m/ β 556.96 (M+B)*, 578.92 (M +Na)+. Example 32

Synthesis of iffo&ug X-AI-PMS: CDI (4 g, 24,7 mmol) was added to a solution of M -2c (4 g, 15.\$ mmo3) in THF (30 mL) and stiffed at RT for 2 ,h. Then a solution of gabapentifl (4 g, 23.4 mmol) ÏQ 20 % NaHCO 3 solution (10 mL) was added and stiixed overnight at RT. The reaction nút Ote was nerct∑lized with 0.5N HCl (pH ~ 4), extracted

with EtOAc (4 x 40 *ml*). dried over Na₂SO*, concentrated end purified by column chromatography to afford 4.7 g (66 %) of I-S12-PD2 as a colorless oil 1 H NMR (300 MHz, CDCl₃): δ 1.45-1.49 (bf s, 19H), 2.35 ϵ 2H)₅ 2.80-2.97 (m, 4H)₅ 3.24 (d, J = 5.7 Hs, 2H), 3.46 (an, 2H) 4.33 (t, J * 5.7 Hz, 2H), 5.0 (br s, IH), 5.71 (br s, IH). MS: (rø/z) [ES]" 449.1 (M-Hf; [ESf 451.2 [M+Hf,

EtOAc saturated wi& HCl gas (5mL) was added to 1-S12-PD2 (0.55 g, 1,22 ramol) attd stored at RT for 10 h. Solvent was removed under reduced pressure and purified by preparative HPLC to give 425 mg (90 %) of \ddot{I} -A1-PD18 as a colotl β s liquid. ¹H NMR (300 MHz, CD_3OV): δ 1.52 (br s, 10H)₉ 2.4 (s, 2H), 2.98-3.0? (m, 4H)₅ 3.27-334 (ra, 2H), 3.61 (s, 2H), 4,5 (t, J = 6.0 Hz, 2H). MS: [ES]⁺ mfe 351.0 [M+Hf, Example 33

Synthesis of prodrug I-A2-PD1: To a solution of levetiracetam (LO g_s, 5.87 mmol) *in* DCE (20 mL) attd DCM (4 mL) was added oxalyl chloride (0.61 *xriL*, 7.05 mmol), and heated at 70 °C fox 8h. Reaction mixture was cooled and added to a solution of SL-X (1,81 g, π.75 tnmol) in DCM (15 JHL) *axnd* stiirtd at RT overnight. After chromatographic purification, 143 g (41%) of I-A2-PD1 were obtained. ¹H NMR (CDCli, 300 MHz): 8 (ppm): 0.8? (t, J = 7.3 Hz, 3H), ï.84-2.04 (π₂, 4H,), 2,41 (t, J = 6.9 Hz, *m.*) > 2.69 (bs, IH)₅2.87-2.95 (m, 4H), 3,02-3.11 (m, IH), 3.65-3.75 (m, IH), 3.85-3,95 (m, 2H), 4.06-4.12 (m, IH)₁ 4.34-4.41 (m, 2H), 8.69 (bs₉ IH). MS: (ES⁺): m/z 351.0 [M+Hf; 372.9CW^Na]⁺.

Example 34

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Synthesis of prodrug I-A3-PD1: To a solution of I-S13-JPP1 (which was syntheaaecl as described in Example 37, Step 2) (215 mg₉ 0.292 mmol) *and* trUsopropylsilanc (60 µL) in 0.75 mL of DCM was added 20 % TFA in BCM (0.5 nOL) and stirred at RT for 90 min.

The mixture was concentrated and the residue purified by column ctøomatøgrapJby to give SS mg (46%) of I~A3-røl, 1 H-NMR (300 MHz₅ CDCl₃): 5 2.51 (S, 3H)>2-8S-2.92 (m, 4H), 3.87 (t, 2H, J - 4.5 Hi), 4,37 (t, 2H, J = 6.0 Hz), 7.25-7.43 (m, 7H), 8.01 (d, 2H, J - 3,0 Hz). MS ($^{\circ}$ i/z): 493 [M-HT, 517 pd+Naf .

Example 35

30 Synthesis of prodrugs ï-A3-PP3a and I-A3-FJ)3fc Step 1: PSC \$10 m & 0.824 mmol) and TEA (0.230 i»L₂ 1.64 xrøaol) were added to a solution of methyl £(2")

hydroxyethyl)diti3io]acetate (IOOmg, 0.549 mmol) in acetonittile (1 mL) at 0 ⁰C and stirred at RT for 3h, The joixture was concentrated and ihc residue dissolved in DCM. Usual aqueous work-up and chromatographic purification gave the crude intermediate.

Step 2: TEA (24mg, 0.236 rmnoi) and DMAP (13 mg) were added to a mixture of valdecoxib (62mg, 0.195 $t\pi$ mol) and the product obtained from step 1 above in THF (1 Π L) and sti π ed at JtT for 3 4 The mixture was concentrated and the residue dissolved in EtOAc After usual aqueous work-up and chromatographic purification, 53 mg (52%) of 1-A3-P03a obtained. ¹H- NMR (300 MHz, CDCl₃); δ 2.51 (s, 3H). 2.97 (t, 2H_>J * 6.0 Hz), 3,48 (S₃2H), 3.76 (s, 3H), 437 (t, 2H, J = 6,0 Hz), 733-7.40 (m, IB), 8.03-8.12 (m,

Step 3; The above material was converted b the corresponding mono-, and/of di-soditixø salt foir Cs I-A3-FD3b by using standard methods. Thus, to a cold solution of the above compound (150 ing, 0.287 ramol) in THF (1 mL) was added IM LiOH solution (28 mg \ddot{u} ImL water) and stirred overnight at RT, The mixture was concentrated, the residue diluted with water, acidified with IKf HCl (~3 mj, pH ~3) and extracted wifli EtOAc. After usual aqueous wotMip and chromatographic purification^ 20 mg (13%) of product were obtained. 1 H- NMR (300 MHz $_3$ CDCl $_3$); δ 2.49 (s $_2$ 3H), 2.70-2.89 (m, 4M), 4.23-433 (m, 2H), 7.28-7,38 (% 7H) $_3$ 8.01-8.03 (m, 2H).

Example 36

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20 Synthesis of prodrug I-A3-FD4: This prodrug was synihosized as described in Sclrønes 13, Method B.

Step 1: Synthesis of mteπnediate LI-8;

2H), MS (m/z): 521 [M-H].

CDI (1.65 & 10.19 tmol) was added to a solution of 3Ut-Ia (2.0 g» 10.19 mmol) b DMF (10 jaL) and stirred at RT fcrf 3 h. 'M,N-Djmeihylethyl«aediarome (1.2 mL, 11.J2 rømol) was added and stirred for 2 h. The mkt Ote -was concentrated and the residue taken up itt EtOAc. After usual aqueous wojrk-up and chromatogfapWc purification, 1.3 g (41%) U-S were obtained. ¹H-NMR (300 MH* CDCl₃): δ 2.07 (s, 3H), 231 (bs, 6H), 2.51 (t, 2H₃ J = 6.0 U2% 2.91 (t, 4H, J « 6.0 Hz), 331 (q, 2H, J * 6.0 Hz), 4.28-4.34 (m, 4H), 5.52 (b% IH).MS (m/z): 333 IM+Naf.

30 Step 2: Synthesis of jπtexmediate *tl-9*: To a solution of Ll-θ (13 %4-18 mmol) in MeOH (7 mL) was added a 1.25M solution of K₂CO₃ (5 mL) and stilted at RT for Ih.

TJte mixture was concettrat β t and tijte residue was *taken* up a DCM. After usual aqueous work-up, 1-0z g (91%) of product were obtained. ¹H-NMR (300 MHz, CDCli₃), δ 2.29 (s, 6H), 2.54 (t, 2H, J * 6.0 Hz), 2.86-2.99 (m, 4H), 3.33 (q, 2H, J = 5.0 Hx), 3.86 (t, 2H, J * 6.0 Bz), 4.31 (t, 2H, J = 6.0 Ha) 15.71 (bs, IH), MS (mfe): 269 [M+Hf. This product was used as such in the next *step*.

Step 3: Sjtøthesis of intejmedi&te LMO; A solution of I£9 (1.02 & 3,80 mmol) in ac tonitrile (10 mL) was added Io a cold solution of DSC (1.46 g, 5JO mmoi) in icetonjtrile (50 mL) followed by TEA (1.58 nil, 11.40 mmol), and stirred overnight at RT. The mixture was concentrated and the residue was takeft up in DCM. After usual aqueous work-up, 1.33 g (85%) of W-10 were obtained-

Step 4: Synthesis of I-A3-PD4: TEA (0 A94 jonL, U 9 mmol) and DMAP (73 tog, 0.6 noMol) were added to a solution of H-10 (1.33 g, 3.24 mmol) and vaïdecoxib (364 mg, 1.16 ramrøl) in THF (6 mL) and strøed at RT for 5 d. The waxtore was concentrated and the jesidue was taken, up in DCM, After usual aqueous work-up and chromatographic

purification, 177 mg (12 %) of LMO were obtained 1 H-NMR (300 MHz, CDCl₃): δ 2.46 (s, 3H)₅2.85-2.95 (in, WH), 3.28 (t, 2H, J - 6.0 Hz), 3.65 tø, 2H, J - 3.0 Hz), 4,22-4.28 (TO, 4H), 7,22-7.41 (tn, 7H), 7,94 (d, 2H_•J * 9.0 Hz). MS (m/z): 609 [M+H] ⁺. This produfct was converted b water-soluble hydrochloride salt form using standard methods. Example 37

20 Synthesis of prødmg I-A3-PD5: This prodrug was synfilesized as shown in Scheme 13.

MβhodB.-

Step 1: Syaβtesis of prodrug iirteiroediata LHsy: -

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A sotodoa of U-U (1.0 g, 2.52 xamoT) in acctoutdle (10 mL) was added b a solution of DSC (Q.96 g, 3.78 ramol) in acctonitrile (20 mL) and stirred for 10 mia, A β er cooling to 0 °C, TBA (1 ml, 7.57 ramol) was added mid stirred at KT for 3.S h. The solution was concentrated and the residue was taken up in DCM. After usual aqueous work-up, the crude product obtained was used as such in the next step.

Step 2." Synthesis of prodrug intermediate 1*S13-PD1: A mixture of the above intermediate (2.5 ml) and valdecoxib (280 mg, 0.892 mmol)., DMAP (56 jtng, 0.5 tamo i) and TEA (ISO μ L_> 1.06 mmol) in THF (5 mL) was sti π ed at RT for 4.5 d. The mixture was concentrated and the residue dissolved ia EtOAc After usual aqueous woric-up and chromatographic purification, 354 mg (54 %) of I-SU-H»i wei β obtained. ¹H-NMR POO MHz, CDCJ₃): 8 2.47 (s, 3H)₃ 3.32-3.41 tøi, 4H), 4.28 (i, 2H, J = 6.0 Hz), 4.47 % 2H, J - 6.0 HzX 7.20-7.61 (m, 22H), 8,00 (d, 2H_>I - 9.0 Hz). MS (Π J/z); 736 [M-HI".

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Step 3; Syirtfotssis of iijte π ncdiate \ddot{l} -A3-PD1: To a solution of \ddot{l} -S 13-PD1 (215 mg, 0.292 mmo) and twisopropyls HaOe (60 μ L) Ui 0.75 ml of DCM was added 20VoTPA in DCM (0.5 mL) and stii \ddot{l} at RT for 90 man. The mixture was concentrated and the residue purified by column ehromMogrophy to give 65 mg (46%) oFI-A3-PDI. l H-NMR. (300 MHz, l CPa l ; 8 2.51 (s, 3H) 2.85-2.92 (m, 4H), 3.87 (t, 2H l J «*4.5 Hz), 4,37 <t, 2H, J - 4.5 Hz), 7.25-7,43 (m, 7H), 8,01 (d, 2H, J « 3,0 Hz). MS (m/z); 493 [M-HJ; 517 [M+Na]*.

Step 4: Synthesis of I-A3-PD_ ï-Me-ester CUI (40mg > 0.243 mmol) -was added to a solution of Ï-A3-PD1 (100mg» 0.202 irorool) in DMF (0,5 mh) amd sttπred at RT for 2.5 b-To this were added a solution of dimethyl ghrtaroate (53 mg, 0.303 ωmol) Jn DMF (OJ IDL) and DMA? (37 mg, 0,303 BHÏvQI) and stiwed overnight at RT. The mixture was dissolved in EtOAc and, after roial aqueous wotk-ujp fatd chromatographic purification,

25 110 mg ("78%) of I-A3-£D5-!Wfe-es*er wets obtained *H- NMR (300 MHz, CDCI₃); δ 1.71-1.91 (m, 2H), 2.38-2.42 (m, 2H), 2.44 («, 3H), 2.84-2.95 (m, 4H), 3-66 & 3H), 3.67 <s, 3H), 4.3M.34 (m, 4 \ddot{l} T), 4.43^t.52 (m, IH) $_3$ 7.31-7.41 (m, 7H), 8.02 & 2H, J = 9.0 Bz). MS (H \ddot{l} Z): 694 [M-H] ".

Step 5: Synthesis of prodrug I"z43«PDS: IK tithi On bydroxide (1,2 mL, 12 mmol) was

30 added b a societion of I-A3-yD5-Me- Bst br (100 mg, 0.144 mmol) in THF (0.4 rel.) at 0

OC and the mixtuife allowed b attain, ambient temperature. After 30 mm, the mixture "was

concentrated and the residue diluted with water. Acidification with IN HC], followed by extraction with EtOAc, usual aqueous work-up and chromatographic purification gave 26 mg (26%) of I-A3-PD5, 1 H-NMR (300 M $^{\circ}$ fe, CP $_{3}$ OD); δ U 2.1.97 (m, IH), 2.05-2.13 (m, *IB*), 2.30-2.40 fi 2H), 2.48 (s, 3H), 2.84 - 2.94 tø, 4H), 4,06 - 4,08 (m, JH), 4.15 \sim 4.22 Ow, 4H), 7.30 (d, 2H $_{S}$ J « 9 Hz), 7.35 - 7.41 (ro, 5H), 7.92 (d, 2H, J - 9,0 Hz). MS (μ/z) : 666 JM-HJ $^{\circ}$.

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Syndesis of prodrug H ï1-HH: This prodrug was spithesized as shown in Scheme 14, tøet üodB.

- Step 1: A solution of metronidazole (5,0 g, 29.22 mmol) and CDi (5,21 g_> 32.2 mmol) ia DCM (100 HiL) was stored overnight at RT. After usual aqueous work-tψ, 7,32 g of the iwiidø2DlMe of metronidazole were obta üed, which was used as such in the t βxt step. Step 2: A solution of the imidrøolide of wietronidazole (7,32 g) in OMF (30 raL) was adcM to a solution of SIrI (6.39 g_> 41.43 mjnol) in DMF (10 triL) and stirred at 60 °C for 2.5 h. The mixture was concentrated and die Jtsidue was taken up in DCM- After usual aqueous worfc-ujp and chromatographic purification, 6.32 g (65%) of I-H1-PD1 were obtained. ¹H-NMR (300 Mfe, CDC]₃): δ2.15 (bs, IH), 2.52 (s, 3H), 2.83-2-S2 (m, 4H)₅ 3.84-3.92 (JH, 2H), 4.34 (t, 2H, J = 6.0 Hz), 4.SI (t, 2H_S J 3-0 Hz), 4.534,62 (m, 2H), 7.% (s, IH).
- Example 39
 Synthesis of I-HJ-PD14: This prodrug was s^nuthesfeed as described itt Scheme 14, Method C. Thus, TEA (0.915 mL, 6,36 rømol) and DMAP (cst) were added to a solution of U-2C.TFA (541 tttg, 3.94 mmoi) and the injidazoüda of metronidazole (synthesis described in Example 114) (870 mg, 3,28 mmol) in DMF (2 mL) and the mixture was heated at 60 'C for 3.5 h- The roixtttre was concemøated and the residue, after usual aqueous work-up and chromatographic jairificatioo, gave 546 mg (48%) of I-HI-PDH

 1/H-NMR (300 MHz, CDCl₃): S 2,48 & 3H), 2J6-2S6 (m, 4H), 3.46 (q, 2H, J = 6.0 Vz% 3-87 (t, 2H, J « 6.0 Hz), 4.41 (t, 2H, J « 6.0 Hz), 4.57 (t, 2H₉ J * 4.5 Hz), 7.90 (S₃ IH). MS (m/z): 351[M^H]⁺.
- **30** Example 40

Synthesis of prodrug **I-H1-PD2**: This prodrug was synthesized as described in Scheme 14, Method C. *Thus*, CDI (180 *tag*, 1.1 mmol) ø added to a solution of I-ÏBUPD14 (350 fflgj 1.0 mmol) in DMF (2 raL) and stirred at RT for 4 h, N₂N-DiniethylethylenedianiiRB (88 mg, 1.0 mmol) was added and stiired for 3 h. The mixture was concentrated and the residue purified by column chromatography to afford 175 mg (38%) of HW-P02. ¹H-NMR (300 MHz₅ CDCl₃): δ2.28 (s, 3H). 2.49 (s, 61\$, 2,51-2,55 (m, 2H)₃ 2.81 (t₂2H, J - 6.0 Hz), 2-89 (t, 2H, J * 6.0 Hz), 3.27-3.33 (m, 2H), 3.46 (q, 2H, J = 6.0 Hz), 4.29 (t, 2H, J * 6.0 Hz), 4.40 (t, 2H, J = 4.5 Hz), 4.57 (t₂2H, J « 4.5 *Mz*), 5.55 (bs, IH), 7.94 (s, IH). MS (m/z): 465[M+Hf. This product was converted to watersoluble hydrochloride salt form using a standard method.

Example 41

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Synthesis of prodrug I-HI-IPDS: Tfcds prodrug \(\hat{\lambda} \) as synthesized as described \(\hat{\text{m}} \) Scheme 14, MeUiOdA.

Step 1: Synthesis of Intermediate I-S14-PD1: A solution of Hue imidaz σHde of M-Ic (Ï.6 g_t 2.98 ram σI) in acetonitrile (10 mL) was added to a solution of Andovudine Ø ,Ø g, 3.74 mmol) was afcetous frile (20 mL) at RT, followed by DMAP (0.914 g, 7.48 mmol) and stirred for 24 h. The mixture was coaceatrated and &c residue, after usual aqueous work—up and chromatographic purification, gave L62 g (79%) of intemiecliate H SÏ 4-PU1, H-NMR (300 MHz, CDCl₃): δ 1.95 (s, 3H), 2.35*2.45 (m, 2H), 2.7S (t, 2H₂J= 6.6 Hz), 2.87 (t, 2H, J⁶ 6.33 Hz), 3.3S (t, 2H, J= 6.33 Hz), 4.05 fa, IH), 4,25 (m, IH), 4.35 - 4.41 (m, 4H), 6,20 (t, IH, J= 6.16), 7,21- 733 (m, 9H)_? 7.42-7.48 (m, 6H) and 8.49 (s, JH). MS Oofe); 712 JMtNa) +.

Step 2: Syixthesis of I-H1-FDS: To a solution of I-S14-PD1 In DCM (15 mL) were added triisoptopylsUane (0.446 ml, 2.17 π rartol), followed by 10% TFA in DCM (15 mL) $m\dot{\alpha}$ stixred at RT for 30 min. The mixture was concenirated and purified by column chromatography be a fibred OM g (70%) of prodrug X-H1-PD5. ^1H-NMR (300 MHz_1 CDCl₃); 6 1.93 (s₇ 3H), 2.30 (bs, IH), 2.41-2.48 $(m, 2E)_f$ 2.88 (t, 2H, J- 6.1 Hz), 2.96 & 2H, J* 6.6 Hz), 3.88 (t, 2H, J= 5.8 H^), 4.05 (rø, IH), 4.29 (m» IH), 4.304.48 (m, 4H), 6.18 (t, la J¹ 6.3 Hz), 7.34 (s, IH) Mud 9.U (s₃ IH)- MS (w/z): 448 tM+Hf, 470 [M+Naf.

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Synthesis of prodrug I-S22-PIM: Hijs prodrug was synthesized m two steps as shown in Scheme^.

Step 1: To a solution of diphosgene (0.35 mL, 2.93 mraol) in DCM QmL) was added a 5 solution of U-Id (0.404 jag, 1.75 mmol), Hurag's base (0.765 JML, 4.39 mmol) and the resulting mixture was stored at RT for 45 min. The mixture was concentrated, the residue dissolved in DCM (5 mL), cooled in an ice-bath and treated with a solution of paciita χ el (500 røg, 0,585 mntol), HuQig's base (0.765 mL, 4.39 mural) and DMAP (cat.) in DCM (5 mL) over 5 mjii and the resulting mixture was sfoed at RT for 2 h. The mixture was purified by column ckomatog Sophy to give 519 mg (78%) of the protected interøicdiate \$22-12 as an off-white solid, ¹H NMR (500 MHz, CDCl₃): 5 1.14 (s 3H), 1.28 (s, 3H), 1.68 (s, 3HX 2.04 (£, 3H), 2.23 (s, 3H), 2.37 - 2.45 (m, 2H), 2.46 (s, 3H), 2.50 - 2.52 (ax, 2H), 2.90 - 2.95 (m₅4H), 3.82 (d, IH» J * 7.0 Hz), 4.05 (s, 2H), 4.21 (d, IH₅J - 8-5 Hz), 4.32 (d, IH, J - 8.0 Hz), 4.40 - 4.42 (m, 5H), 4.97 (d, IH₅J « 9.5 Hr), 5.29 (s, IH), 5.43 (d, $IH_2 J - 2.5 Hz$), 5.69 (d, $IH_1 J = 1.0 Hz$), 6.00 (dd, $IH_2 J - 9.5 Hz$, 2.5 Hz), 6.26-6.29 On, 2H), 7.02 (d, IH, J*= 9.5 Hz), 7.38 - 7.61 (m, UH), 7.75 (d, 2H, J - 7.5 Hz), S.15 (d, 2H, J = 7.5 Ht).

Step 2: To an ice-cold solution of S22-12 (60 mg 0.0532 mmol) in MeOH (1 mL) was added 2 drops of methanol saturated with ammonia gas and the resulting mixture was stiwed for t h. The reaction mixture was purified by column chromatography to give 38 mg (69%) of I-S22-WM as an off white solid. ${}^{1}KNMR$ (500 MHz, CDCl₃): δ L14 (s, 3H), 1.23 (s, 3H), 1.68 (s, 3H), 1.91 (s, 3H), 2.23 (s, 3H), 2.3S - 2.42 (m, 2H), 2.46 (s, 3H), £50 - 2.58 (m₂2H), 2.84 (t, 2H, J = 5.4 Hz), 2.94 (t, 2H, J = 6.5 Hz), 3.82 (t, 3a J = 5.4 Hz), 2.95 (t, 2H, J = 6.5 Hz), 3.82 (t, 3a J = 6.5 Hz) $6.0 H_2$), 4.20 (d, $1H_5J - 8.5 Hz$), 4.31 (d, $1H_8J - 8.5 Hz$), 4.35 - 4.41 (m, 3H), 4.97 (d, IH, J = 7.5 Hz), 5-44 (d, IH, J = 2.5 Hz), 5.69 (d, IH, 7.0 Hz), 6.0 (dd, IH, J = 9.25 Hz, 2.25 Hz), 6.22-6.29 (m, 2H), 7,08 (d, IH, J - 9.5 Kfe), 7.36-7.60 (m, UK), 7.78 (4 2H> J = 7.5 Hz), 8.14 (d, 2H, J - 7.5 Hz).

Example 43

Synthesis of prodrug I-S22-PD2t To a solution of I-S22-FD1 (38 mg, 0.0367 mmol) in acetonitrile (0,6 mL) was added succinic anhydride (5 mg, 0.044 xmool) and DMA? (cat). The resulting mixture was stiired overnight at RT and purified by column

chromatography to give 12 røg (29%) of prodrug \ddot{I} -S22-PD2 as an o# white solid. *H NMR (500 MHz, CDCl₃): δ 1.14 (s, 3H), 1.2\$ (s, 3H), 1-68 (s, 3H), 1.91 (s, 3H), 2.22 (s, 3H), 2.36 - 2.41 (m, IH), 2.49 (s, 3H), 2.57 - 2,63 (m, 53H), 2.86 - 2.89 (m, 2H), 2.93 (t, 2H_SJ* 6.5 Hz), 3.79 (d, IH, J* 7.0 ffe), 4.20 - 4.44 (ra, 7H), 4.98 (4 IH, J = 8.0 Hz), 5.53 (d, IH, 3.0 Hz)₃ 5.69 (d, IH, J* 7.0 Hz), 6.02 (dd, IH, J=>9.5 Hz, J= 3.0 Hz)₃ 6.26 . 6.29 (rø, 2H), 7,20 (d, IH₅J= 9.0 Hz), 7.33 - 7,62 (m, UH), 7.74 (d, 2H, J - 7.5 Hz), 8.14 (d, 2H₃J - 7.5 Hz). MS (ES†) $m\dot{\uparrow}z$ 1134.44 [M+Hf; 1156.56 [M+Na]*.

Water solubility: Paditax β 1 and its prodrug 1-1522-1*302 (2 mg each) were suspended in 1 iuL water or ?BS-buffer (pH 7.4). The suspensions wtie sonicated fox 15 min and centrif Ogcd (13,000 g) fbi 10 mia. The smpematant vras analyzed using HPLC.

H?LC: Waters RPIS cotrøtt* (150 x 3.9 mM, X-T« πa); DAD-HP Agilent (Model 1100); elueat'. CH₃CN;H?.O (gradient 0-100% acetonitrilein 045 min). The uv-detector was set at 210 nM. The concentration was determined by measuring the relative area of pacHtaxel or I-S22-PD2. It was observed that the solubility of I-S22-PD2 was 20 times more than & at of paclitaxel. (i.e, -0.2 mg/mL).

The foHpving double/mutual prodrugs (Examples 44 - 80) were synthesized by the mtetHods depicted in Schemes 17-2 t susing appropriate therapeutic agents and obvious modifications:

Example 44

Synthesis of mutual prodrug of desloratidine and pscudoqphedrine (I-AA-MPDI): This iitutual pxodmg was gynttvesized as depicted in Scheme 21. The compound \ddot{i} -AA,-MPDI was obtained as a colorless gum. 1 H-NMR (300 MHa, CDGt₃): δ LOO (d, 3E, J = 6.9, Hz) $_{5}$ 2.27-2.51 <m, 4H), 2.74-2.97 (to, 9H), 3.2S-3.4t(m $_{1}$ 4H), 3.79 (bs, 2H), 4.28-4.30 <m, 4H), 4.57 (m, IH), 7.04-7.44 (m, 9H), S.26-S.33 (m, 2H). MS (m/?): 682

25 [M+Hf.

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Example 45

Synthesis of mutøal prodrug of amlodipine and Itsinopril ((-AA-MFDJ):

Step 1: Synthesis of diethyl ester of lisin Opril:

To a suspension of lisinop πl (10.0 g, 22.62 mmoX) in ethanol (150 mt) was added SOCl₂
 30 (4.95 wiL, 67.94 ramol) and reflused for 1.5 h. An additional 1 wL of SOCh was added lo the mixture every hour for 4 h. The mixture was concentrated and azeotroped with

benzene. The resulting hydrochloride was basifled with saturated NaHCO $_3$ and extracted with EtOAc. Usual aqueous work-up gave 12.86 g of Usin optt diethyl ester, which was used without purification. 1 H-NMR (300 MHz, CDCI $_3$): δ 1,23-1.64 (m, 10H), 1.89-2,3 (BR, 6H), 2.63-2.66 (m, 2H), 2.80 (bs, 2H), 3.19 (t, 2H, J * 7.5 Mz), 3.364.59 (m, 6H), 4.12-4.19 (m, 4H), 4.4-4.5 (m, IH), 7.14-7,28 (m, 5H). MS [m/z]: 462.4 $\{M+Hf\}$.

Step 2; Synthesis of Ï-AA-MPP2: CDI (1.23 g, 7.64 romol) was added to a solution of Ï-A1-PD2 (Example 18) (3.0 g, 5.09 mmol) in DMF (10 mL) and stirred RT for 3.5 L A solution of Hsinøpril diethyl ester (2.34 g, 5.09 mmol) in DMF (5 mL) was added and stirred at 65 °C for 8 h. The reaction was quenched with brine and taken up in EtOAc.

After usual aqueous woik-up and cliromatographic purification, 2.5 g (45%) of J-AA-MP02 were obtained. 1 H-NMR (300 MHz₃ COd_3): δ 1.17 (t, 3H₂J ~ 7,5 Hz), 1.24-1.30 (m, 7H), 1.45-1.80 (m, 7H), 1.90-2.30 (m, 7H), 236 (s, 3H), 2.70 (bs, 2H)₂2.89-2.95 {m, 4H)₅3.10-3.20 (bs, 3H), 3.40-3.70 (m, 9H), 4.00-4,40 (m, 10H)_y4,47-4.53 (m, IH), 4.68-4,73 (q, 2H, J - 13 EzI 5.30 (bs, IH), 5.39 (s, IM), 5.65 ϕ MH), 7,15-736 (tn, 9H). MS (m/z): 1076 [M+Hf, 1098 [M+Naf,

Example 46

Synthesis of mutual prodrug of amlodipine and Josartan (I-AA-MPrøa);

This mutual prodrug was synthesized as described in Example 34, with obvious modifications, using the appropriate ammo cootaiui π g therapeutic agents. The pxoduct 1-

20 AA-MPR3n was obtained as a cream color soK4 ¹H-NMR (300 MHz, CDCI3): δ 0,86 (t, 3H, J = 6.6Hz), 1.16 fl, 3H, J = $^{\circ}$ 7.1 Hz), 1.31 (m,2H), 1.60 (m, 2H), 231 (s, 3H), Z48 <t, 2H, J = 7.9 Hz), 2.804.92 (rø, 4H)₄ 3,40 (m, 4H), 3.56 (s, 3H), 4,01 (m, 2H)» 432 (m, 4H), 4.6S (q, 2H, I - 6.5 Hz), 5.00 (s, 2H), 5.14 (5, 2H), 5.37 (s_f IH), 6.90 (d, IH, J = 7.8 Hz), 7.02- 7.22 (m, 5H), 7.33-7.43 (m, 3H), 7.50-7.60 (m, 2H). MS (QJ/Z); 1037 [M-H] ",

25 Example 47

Syndesis of smutuadl proding of ceie to: jb and valdecosib (U-AA-MPD4):

This mutual prodrug was synthesized by reacting the imidazoline intermediate of I-A3-PPJ -with valdecoxib according to method described in Scheme 17 with appropriate modifications. This mutual prodrug I-AA-MPD4 was obtained as a white solid. JH-NMR

30 (300 MHz, CDCJ₃); δ 2.16 (s, 3H), 2.29 (s, 3H), 2.71 (bs, 4H), 4.14 (bs, 4H), 6,69 (s, 2H), 7.02-7.33 (m, 14H), 7.97 (d₂3H, J « 9.0 H2)» MS («1/2)1 900 (M-H)".

Example 4\$

Synthesis of double prodrug of vajdecojúb (I-AArltøPDS);

This double prodrug was synthesized by reacting hAS-TDI and vald β coxib using the method B described in Scheme 13, The double prodrug I-AA-MPD5 was obtained as arv off white solid, ¹H-NMR (300 MHz, CDCl₅): δ 2.40 (s, 6H), 2.82 (bs, 4H), 4,20 (bs_>4H)₉ 7.20-7.35 (ÏJI, 14H), 7.97 (d, 4H, J = 9.0 Hz). MS (m/z): 833[M-H]-, Example 49

Synthesis of double prodrug of valdcoxib fl-AA,-MPD8a):

- This mutual prodrug was synthesiaed using succinic anhydride and valdecoxib according to method B described in Scheme 13 *νήih* appropriate modifications. This double prodrug ï-AA-MPDSa w s obtained as an off-vfliite solid. lH-NMR (300 MHz, CDCl₃); 6 2.46 (s., 6H)* 2.58 (s, 4H), 7.25-7.37 (m, WH), 7.95 (d, 2H, J = 9.0 Hz). MS (rø/z): 709 \M~H\\ Eγaiÿple50
- Synthesis of double prodrug of vatøecoxib (t-A λ-MPDSb):
 This mutual prodrug was synthesized using gNaric anhydride and valdecoxib according to method B described in Scheme J3 with appropriate modifications. This double prodrug I-AΛ-MPD8I> was obtained as a coïortess gum. ¹H-NMR (300MHz, CDCl₃+CD₃OD): δ 1.68-1,74 (wi, 2H), 2,15 (t, 4H, J = 4.S Hz), 2,38 (s, 6H), 7.01 (bs, IH), 7,17-7.30 (m,
- 20 J4H), 7.50 (bs, IH), 7,88 (d, $4H_{>}J = 8.58$ Hz). MS (m/z): 723 pV!-HI\
 Example 51
 - Synthesis of mutual pjodrug of ola&zaptøe and fluoxetine (I-AA-MPD9):
 - This mutual prodrug *vm* ittade according to Scheme 17 with appropriate modifications. This mutual prodrug I-AA-MPP9 was obtained as a yellow gwn. IH-NMR (300 MHE 5
- 25 CDCI₅): δ 2.05-2.20 (ro, 2H), 2-40 (s, 3 $\ddot{\text{II}}$), 2,44 & 3H), 2-50-2.90 (m, 12H), 330-3,80 (ro₅ 4H)₅ 4.10-4.50 (m, 4H), 5.20 (bs, IH)₉ 6.42 & 1H)₇ 6.87 (d, 2H, J 8.52 Hz), 7.04-7,36 (m, 9H), 7,42 (oV2H_s J » 8.67 Hz). MS (m/z); 828 [M+H]⁺. Example S2

Example 32

Ssnathesis of dotible prodrug of gabapentin QtAArWffikO&y.

30 This double prodrug was synthesized as described below:

1

Step 1; A solution of SL-I (3.0 g, 19.4 mmol) in DMF (5 mL) was added to a suspension of CDI (9.46 g, 5,83 mmol) in DMF (15 mL) and stitred at RT for 20 h. The mixture was concentrated and the residue purified by column chromatography. The bis-imidazol ide obtained was used as such in $\dot{\omega}$ e next step.

Step 2: A solution of the bis-imidazotfde (1.0 g, 2.91 mmol) in acetonM o (3 mL) was added to a dispersion of gabape πin (1.49 g, 8.75 mmol) in IN NaHCO₃ (8 mL) and stM at RT for 3 d. The oaixtwe was diluted with water, acidified with 2N HCJ and extracted with EtOAc After usual aqueous work-up and chromatographic purification,, 1.04 g (65%) of pare Ï-M-MPP10 ν∞ obtained. ¹H-NMR (300 MHz, CDCl₃): δ 1.20-1.47 (m, 20H), 233 (s, 4H)₅ 2.96 (t_>4H,-J = 5.48 Hz), 3.23 (d_f 4H, J - 6.5 Hz), 4.31 (t, 4H, J - 6.0 Hz), 5,55 (t, 2H, J * «6.6 Hz), ESI - MS (wite): 547 [M-H]".

Example 53

Synthesis of dotibte prodrug of gabape miix ethyl ester (MA-MPDIOfe):

A mixture of Ï-A1-PD8 (2.0 & 5.26 iranol) and Hunig's base (2.75 πiL, 15.8 mmol) in DCM (S mL) was added to a solution of diphosgette (1.27 mL, 10.53 mmol) in DCM (4 mL) at 0 ¹C and stinted for 30 mia. The mixture was concentrated, dissolved in DCM (10 mL) and treated -with a solution of gabapemtin ethyl ester hydrochloride (1.S6 g, 7.8S modol) and Hnoig's base (2.74 mL, 15.77 mmol) in DCM (10 jnL). The mixture was stiired for 3 h. After usual aqueous work-up, the crude material was purified by preparative HPLC to affojtd 2.2 g (69 %) GfI-AA-MPDIOb as a colorless oil ¹H-KMR (300 MHs, CDCl₃): δ 1.25 (t 6H, 3 « 6.0 Hz), 1-35-1.67 (m, 2(B), 2Zl (% 4H), 2.91 (t, 4H, J ^ 6.0 Hz)₉ 3.18 (4 4M, 3 - 6Λ Hz), 4Λ2 (q, 4H, J - 6Λ Hz)₅ 4-29 (to 4 H, J ≈ 6.0 Hz) 5.42 (bs_>2H). MS; ES+ m/z 605 [M+HQ⁺, 627 IM+Naf .

Example 54

Synthesis of mutual prodrug of larootrigine and gabsφeβtin (I-AArMMWI):

To a solution of I-A1-PB4 (4.5 g, 10.32 mmol) in acetonit de (40 tnL) at RT was added CDI (2,0 g, 12.38 mmol) and stored for 3 h. To this -was added a solution of gabapentin (2.12 g, 12.38 mmol) in 10 nil of IZoNaHCO₃ solution and the mixture was stored at RT for 24 h. After usual aqueous worfe-up and chromatographic purification, 2.6 g (40 %) of I-AA-MPDU was obtained as an off white solid. HWMR(CD ₃OD^OOMHZ)I S LH-1.48 (m, 10H)₅2.28 (s, 2H), 2-99 (t, 2H, J - 6.0 Hz), 3.06 (t, 2H, J « 6.3Mz), 3.22 (s, 2H),

4JI (t, 2H> J = 6,0 Hz), 4.46 (t, 2H, J = 6.3 Hz), 7.39-7.49 <m, 2H)₅ 7.69^7.7I ($_m$ > IH). MS: (ES +)m/z 633,1 (M+H)+»655.1 (M +Na)+. Example 55

Synthesis of mutual prodrug of gabapentm ethyl ester and lamotrigme (I-AA-MPD12):

- 5 To a suspension of lamotrigine (2,70 g, 10.55 tnrøol) and PMAP (1,28 g, 10.55 mmol) in tolucue (40 niL) at 1]0 °C was added a solution of the imidazotf de of Ï-A1-PD4 (4.99 g, 10.55 πrøol) THF (20 mL) and stiπed overnight at 110 °C. The reaction Of ixture was purified by column chromatography to afford 0.85 g (12 %) of I-AA-MFD12 as a white solid. ¹ HNMR (CDCl₃, 300 MHz) δ 1,24 (t, 2H, I = 7,2 Hz), L36- 1.77 (m, 10H), 2,29 (s, 2H), 2.93-3.03 (m, 4H), 3.22 (d, 2H₅ J « 6.6 Hz), 44 1 (q, 2H, J » 7.2 Hz), 4.34 (1, 2H₅ L* 6.6 Hz), 447 (t, 2H₅ L* 6.6 Hz), 565 (t, 1H₅), 734.741 (m, 2H), 760-763 (w, 1H)
- J * 6.6 Hz), 4.47 (t, 2H, J=^6,3 Hz), 5,65 (t, IH), 734.7.41 (m, 2H), 7,60-7,63 (w, IH).

 MS: ES+ xnfe ^61 (M+Hf, 682 (M+Na) +.

ExAïaple 56

Example 58

Synthesis of mutual prodrug of gabapeatin ethyl ester and levetiracetam (I-AA-MPI> Ï3);

- To a solution of levetiracetaEQ (1.0 g, 5.87 mmol) in DCE (25 mL) and DCM (5 mL) at RT was added ojcalyl chloride (895 mg, 7.05 mmol). The reaction mixture was refluxed for 5 h, aftø; which it was cooled to RT and a solution of I-Al-PD β (2.67 g, 7.05 rotnol) in DCE (20 jxtL) was added drop-wise. The resulting mixture was stirred at RT for 18 h. After usual aqueous wak-th and chromatographic petrification, 1.63 g (48%) of Ï-AA-
- MPB13 was obtained as a yellow oil ¹H NMR (CDCl ₃, 300 MHz): 5 0.87 % 3H, J * 7.4 Hz) ₉ 1.25 (t, 3H₂ 3 = 7.1 Hz), 1.344.52 <m, 10H), 1.82-2 Λ 1 (m, 4H) _S2.28 (s, 2H), 2,40 (t, 2H, J = 7.0 Hz), 2.89-2.94 (m, 4H), 3.04-3.1H (m, IH) ₁ 3.19 (d, 2H, J = 6.6 Hz), 3.66-3.75 (m, IH), 4,07-4.16 (m, 3H), 4.27-4.35 (in, 4H) ₅ 5.4S (t, IH₂ J = 6.5 Hz), 8.18 (bs» IH). MS: (ES"): xoAs 576.1 [M+Hf; 598. \ddot{I} fM+Najt CBS \dot{I} : mlz 574.2 EM-H]+.
- 25 Example 57
 Synthesis of mutual prodrug of gatoφ entin eihyl ester and valproic acid d^AA-MP»14):
 TBis mntaή prodrug was guthesized accoiding method outlined in Scheme 18. This mutual prodrug I-AA-MPDH4 was obtained as oil. MS (m/z): 592 [M+Hf].
- 30 Synthesis of mutual prodrug of gabapentin & 1 estejc and valproic acid (I-AA-MPDIS):

This mutual prodrug was synthesized according to the method outlined in Scheme 18. The mutual prodrug \ddot{l} -M-MPD15 was obtained as a yellow oil MS (m/z)t 620 [M+Hf . Example 59

Synthesis of mutud prodrug of gabapentin ewyl ester and valproic acid (I~AA-MW)16):

- To a suspension of V-Φ jrøtnide (750 mg. 5.24 røraol) sn PCE (15 of L) at 0.5 °C was added oxalyl chloride (0.5 mL₃ 6,29 mmol) and iefiuxed overnight. The inaction mixture was cooled to RT, treated with a solution of I-A1-?D8 (2.18 g, 5.76 nwnol) in DCE (2 mL) and stirred at RT for 2 h. The reaction mixture was purified by column chromatography to afford 1.61 g (51%) of I-ΛA-MPD16 as a colorless oil. ¹H NMR (CDCl₃, 300 MHz): 5 0,89 (t, 6H, J 7.09 Bz), 1.25 (% 3R, 3 = 6.96 Hz), 1.31-1-69 (m_>
- 10 (CDCl₃, 300 MHz): 5 0,89 (t, 6H, J 7.09 Bz), 1.25 % 3R, 3 = 6.96 Hz), 1.31-1-69 (m_> 18H), 2.29 (s, 3H), 2.89-2.99 (m, 4EQ, 3.20 (d_s 2H, S 6,47 Hz), 4.13 (q, 2H)₅ 4,33 (t, 2H₅ J 6.71 Hz), 4.40 (t, 2H, J = 5.97 Hz), 5.54 (t, IH), 8.29 (br s, IH). MS; ES+ mfe 549 [M+Hf, 571 [M+Na]*.

)Eiaiπplc60

- 15 Synthesis of double prodrug of valproic acid (I-AA-MEDM):
 - To a suspension of valpromide (3.0 g, 20.95 njfflol) m DCE (30 jnL) at 0-5 0 C -was added oxalyl chloride ($I\Lambda$ mL, 15.08 mmol) and refhixed oveimjight The reaetj \dot{U} n mixture was cooled b RT, a solution of $SI\Lambda$ (0,80S:g, 5.24 tnmol) j» PC)E (3 niL) was added and stiried over Oxfai After usual work-up arid chtoimatogiapbio purification, 1.97 g (43%) of
- 20 I-AA-MPD22 were obtmπed as a white solid. 1 H "NMR (CDCl $_3$, 300 MHz): δ 0.S9 (t, 12H, J * 7.18 Hz), 1.28-1.66 (m, 16H) $_5$ 2.94-2.95 (m, 2H), 3.02 (t, $6tt_f$ 3 ^ 6.S1 Hs), 4.42 (t, 4H $_1$ J « 6.47 Hz). MS; m/a 493.2 [M+Uf, 510.0 {M+NKtf , 515.10 EMWa] $^+$; Example 61
 - Synthesis of mutual prodrug of gabapentin ethyl ester and valproic acid (I"AA-MPP27):
- Step 1: To a solution of I-A1-PD8 (4.0 g, 10.54 mmol) in THF (25 mL) was added CDI (2.22g, 13,7 tnmol) and stirred at RT for 90 min. To this was added t-butyl carbazate (1.39 g, 10.54 mmol) and DMAP (1.288 g, 10.54 mmol), and stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 4.0 g (91%) of the intermediate both-hydrazide was obtained as a colorless gummy material. ¹H NMR.
- 30 (CDCl₃, 300 MHz): δ 1,25 (t, 3H, J * 7.1 Hz), 1.43 (s> 9H), 1.31-1.74 (in, 10H), 2,30 (s,

2H), 2.9O-3 Λ ! (m, 4H)₅3.20 (d, 2H, J \(\tilde{0.6}\) Hz), 4.17 (q, 2H, J = 7.1 Hz), 4.32 (t, 2H₂) = 6.5 Hz)₃4,39 (t, 2H, J = 6.5 Hz), 5.42 (br s, IH), 6.04 (br s, IH), 6.98 (br s, IH).

Step 2: To a solution of the above boohydtaz $\dot{\mathbf{u}}$ (4.0 g, 7.44 mmol) in DCM (20 mL) was added 50% TFA/DCM (10 mL) and strared at RT for Ik DCM was removed under vacuum, the resulting residue triturated with diethyl ether (2 x 20 mL) and dried to give a colorless oil, which was dissolved in THF (20 mL). To the above solution at 0-5 0 C was added TEA (2.1 vxU 14.88 romol), valproic acid (1.18 g, 8.184 mmoi), PCC (2.3 & 11.16 m π xol) and DMAP (0.909 g, 7.44 mmol) and the mixture was stirred overnight at RT, The mixture was filtered, concentrated and purified by cohifloa chromatography to afford 2.59 g (51 %) of **I-AA-MPD27** as a, colorless gummy material. 1 H NMR (CDCl₃, 300 MHz): δ 0.85 (t, 6H, J $^{\circ}$ 7.2 Hz), 1.3 (t, 6H, J $^{\circ}$ 7.11 Hz), 1.2M.80 (m, 26H), 2.2-2.3 (m, IH), 2.35 (s, 2H), 2.81-2.94 (m, 4R), 3.21 (d, 2H, J $^{\circ}$ 6.6 i fe), 3.65-3.68 (m, IH), 4.19 (q, 2H, J $^{\circ}$ 7.U Hz), 4.36 (t, 2H, J = 6.51 Hz), 4.39 (t, 2H, J = 6.51 Hz), 5.51 (t, IH), 8.17 (s, IH)- MS: to/*712 [M+Naf. 728 [M+Kf, 68S [M-HJ].

15 Eta ïttple62

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Synthesis of mutual prodrug of valproic acid and mcøtinic acid (I-CC-MPDI):

Step 1: To a soltttioa of iucotiï χ l chl «Sde hydroch Jro Jde (3.16 g, 17.76 mmol) atid $h\ddot{\imath}-2c$ (3 g, 11.84 mmol) in THF (50 mL) was added TEA (8.3 mL, 59-2 jtmuol) $m\dot{\imath}$ stirred overnight at RT. After usual aqueous work-up and chromatographic pmificatio α , 4,14 g (97%) of H-2c-nicoti π ate estet was obtained as a colorless oil. HNMR (CDCt α) 300 MH^: δ 1.43 (s, 9H), 2.82 & 2H, J = 6.31 Hz), 3.42-3.48 t α , 2H), 4.62 (t, 2H, J - 6.59 Hz), 7.29-7.33 (m, IH), 8.30 (d. IH, J - 7.95 Hz), 8.73 (dd, IH, J = 4.S6, 1J2 Hz), 9.23 (d, IH, J * 2.13 Hz). MS: ro/z 358 fltf+Hf, 381 {M+Naf, 739 |2M+Kaf}.

Step 2; To a solution of U»2c-i Ucotrøate eater (0.92 g, 2.50 mmol) in DCM (5 mL) was added 50% TFA/DCM (5 mL) and stirred for Ih. Reaction mixture was concentrated and the residual TFA selt was used as such in Step 3.

Step 3: To a solution of valproic acid (0,3? g, 2,56 mmol) in THF (5 rot) was added CDI (0.5 g, 3.08 ir \emptyset COI) and stirred for 2k This was treated with a solution of the above TFA salt, TEA (0.7 mL, 5.13 mmol) and DMAP (50 mg, 0.41 mmol) in THF (10 mL) aftd the mixture was stirred overnight at RT. After tisual aqueous work-up and chromatographic purification, 0.7 g (71%) of **I-CG-MPDI** was obtained as a white solid. H NMR

(CDCl $_3$, 500 MHz): S 0.88 (t, 6H, J - 7 Hz), 1.25-1.59 (m, 8H), 2.06-2.08 ($m_>$ IH) $_1$ 2.86 (t, 2H, J = 6° Hz), 3.05 (t, 2H, J = 7 Hz), 3.58-3.61 (q, 2H, J - 9.0 Hz), 4,63 (t, 2H, J ~ 6.5 Ea), 7.40-7.42 (m, \ddot{I} H), 8,30 (dt, IH, J \Rightarrow 8.0, 2.0 Hz), 8.79 (dd, IH, J - 5.0, 2.0 Hz), 9.23 (d, 1H, J - 0.5 Hz). MS; m/z 385 (M+Hf, 407 [M+Naf, 423 ptf+Kf.

5 Example *63*

Synthesis of mutual ptodmg of valproic acid and nicotinic acid (I-CC-3MPD2);

This mutual prodrug was synthesized as described in Example 62, with obvious modifications, 0.612 g (41%) of I-CC-MPD2 was obtained as a white solid ⁵H NMR (CDO ₃₉ 300 MHz): 6 0.89 (t, 6H, J = 7.23 Hz), 1.24-1.62 (m, 8H), 2.34-2,42 (TO, 1H),

10 2.92 (t, $2H_{>}J \approx 6.83 \text{ Hz})_{5}$ 2M f 2H, J » 6,04 Hz), 3.7S-3.84 (q, $2H_{)_{1}}$ 4.37 (t, $2H_{)_{1}}$ 5 6.79 Hz), 7.36-7.41 6 IH), β ,15 (d, IH, J - 7.92 Hz) $_{5}$ 8.73 (d $_{>}$ 1H, J « 4.78 Hz), 9.02 (s, IH). MS; ja/z 385 [M+H1+, 419 [M+HClf, 383 |M-H]\

Example (\$4

Synthesis of mutual prodrug of zidovudine and la Tuvudine (I-ffl i-MM)!):

Step 1; Synthesis of fotetmediate I-S17-PDX1:

4-Nitcopb.cnyl chlorofo π nate (0,27 g, 1-34 tOtnol) was added to a solution of the I-HI-P»5 (0.4 g, 0.89 mmol) and pyridine (76 μ ^ I ramo!) in DCM (10 fliL) and sfiir β d at RT for 15 h. The mixtire was concentrated and the residue purified by colu π a ctoomatogmphy to give 0,29 g (53%) of I-S17-PDW. ^{I}E -WiR (300 MHz, CDCl $_{3}$); 5

20 1.93 (s, 3H) $_5$ 2.45 (m, 2H), 2.97-3.06 (m, 4H) $_3$ 4.05 (m, 1H), 4.41 (rø $_>$ IH) $_8$ 4.40-4.49 (m, 4H) $_5$ 4,54 (t, 2H, J - 6.5 Hz), 6 Λ 7 (t, IH, J - 6.0 E $_9$, 7.33 (s $_1$ IH) $_5$ 7.39 (d, 2H, I= 4.8 Hz) $_5$ 8.28 (d, 2H, J - 4.8 Hz) and 8.50 (s, 1H). MS ($_8$ /z): 635 [M+Naf .

Step 2: Synthesis of I-HH-MPD1; iaiaivudin© (45 wg, 0.196 π mol) and DMAP (48 mg, 0.39 jttimol) were added to a solution of I-S17-P011 (SO mg, 0.13 mm \mathfrak{C}) in PMF (1.5 wL) and süued at RT for 30 min. The rowrturfc was concentrated and purified by column chromatography \mathfrak{b} give 40 mg (43%) of product I-HH-MPPt IH-NMR (300 MHz, CDCl₃): δ 1.90 (a, 3H). 2.45 (t, 2H₁ J = 6.1 Hz), 105 (t, 43Ht, J ~ 6.2 Hz), 3^20 Cm, 1H), 3.53 (m, 1H), 4.08 (m, 1H), 4304.80 (m, 8H), 5,45 (t, 1H, J = 3.0 HzX 5.90 (d, 1M,

J « 7.5 Hz), 6.17 (t, IH), 6,30 (t, KH), 7.55 (s, IH) and 7.90 (d, IH, J =>7.50 Kz). MS

30 (ja/z): 725 [M+Naf.

25

Synthesis of mutual prodrug of zidovudine aad lamivudme (I-HH-MPD2b);

This mutual prodrug was synthesized according to the method outlined in Scheme 18. Tte mutual prodrug I-HH-MPIWb was obtained as a white solid. 1 H-NMR (300 MHz, CDCl₃): δ 1.97 (s, 3H), 2.42 (m, 2H), 2.90-2.94 (m, 16H)₅ 3.06 (m, IH), 3.40-3.44 (m, 8H), 3.50-3.56 (m, IH), 3.71-3.73 (m₃ IH), 4.95 (m, 1HX 4.27-4.30 (txi, 4H); 4.37-4.49 (m, 4h)₃ 5.32 (t, *IU*, J = 5.1 Hz), 5,83 (d, IH, J - 6.6 Hz)₅ 6.07 (m, IH)₅ 6.33 (bs, IH), 7,20-7,25 (m, IH), 7.74 (m, IH). MS (m/z); 954 (M+Naf .

Example 66

10 Syftfhesis of mutual prodrug of cetirizrae and pseudoephedtin β (KJA-MPD1):

Step ϊ: Synihe's of πtein_ediatfeI-S17-P!) Ϊ1:

This intermediate was prepared by reacting I-CH*D10 with p-nitro pheayl chloxofbimate by a procedure srøitef b th#t described tαExample 64. The desired intermediate Ï-S17-PDU was obtained as a gum, ¹H-NMR (300 MHz, CDCl₃): S 249-2.71 (m. 10H), 2.95 (t,

2H₂ J = 6.6Hz), 3.01 (t, 2H, J ^α 6.5 Hu)₃ 3.73 (bs, ZH), 4.13 (S₁ 2H), 4.22 (s, IH), 4.41 ft, 2H, J = 6.6 H2), 4,53 (t, 2H₁J = 6.6 Hz), 748-7.40 (m, 11 H), 8.28 (d_y2fiς J - 7.1 Hz).

Step 2: The mutual ptodtug I-CA-MPBI was synthesized by reacting intermediate "-S17-PD | 1 wi* psci | doepWtfcJne by a procedure similar to that described in Example 64₂. Step 2. The desired mutual prodrug | CA-MEDI | was obtained as a colorless granmy

20 material ³H-NMR (300 MHz, CDCl₃): S 0.994,09 (d, 3H, J - 6,6 Hz), 2.45 (bs, 4H), 2.68 (bs, 6H). 2.90 (s, 3H), 2.91-2.94 & 4H), 3.71 (bs, 3H), 441 (s, 2Ify 4.18 (s_s IH), 4.26-4.41 0», 4H), 4.56 (m, 2H), 7.17- 7,35 (m_a UH). MS (m/z): 716 (M+ H]⁺.

Example 67

Synthesis of mutual produng of gabapentin ethyl rater and naproxen (Ï-CA-MPD5):

TWs mutual prodrug was synthesized by reacting I-AI-PD8 and Naproxen UsIng Scheme i I, Method B, This mutual prodrug was obtained as colorless oil. H-KMR (300 ME δ, CDCl₃): δ 1.25 f 3H, J~7.1 Hz)* 1.30-1.55 (m, 10H), L57 (i 3H, J - 7·1 Hz), 2-27 (s, 2H), 2.S4 (fy 4H, J - 6.4 Hz), 3.18 (d, 2H₇J - 6.7 Hz), 3.80-3.88 (m, IH), 3.91 (β, 3H)» 4.12 (q, 2H, J « 7.1 Hz), 4.20-4.40 (m, 4H), 5.35 (H IH), 7.05-7.20 (m, 2H)₃ 739 (dd, 1H₅J * 1.8 Hz, S.4 Hx), 7.60.7.73 (m_>3H). MS (HJ/Z); 592 fM+H]*, 614 [M+Naf.

Syndesis of mutual prodrug of valproic acid and nicotinic acid (Ï-CA-MPD14):

This mutual prodrug was synthesized using valproate and nicotmyl chloride hydrochloride, according to the methods described in Scheme 13 and Scheme 17, with obvious modifications. 1.0 g of the mutual prodrug \ddot{I} -CA-MPDW was obtained as a yellow oil. 1 H NMR (CD₃OD, 300 MBz): δ 0.87 (t, 6H, J = 6 Hz)_s 1.26-1.75 (m, 9H), 2.83 (s, IH), 2.95-3.0 (m, 4H), 3.81 (t, 2H, J * 6 Hz)₃ 4.44 (t, 2H, J = 6 Hz), 7.0 (s, IH), 7.4 (bs, IH), 7.42 (ra, IH), 8.20 (d, IH), 8.6S-8.74 (bs, 2H), £ 0 (s, IH). MS: ES⁺ jn/z 428.1 fM+Hf, 450.1 [M+Na]⁺.

10 Example 69

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Synthesis of mutual prodrug of valproic acid and, nicotinic acid (Ï-CA.-MPDX5):

To a solution of **I-C1-PD13** (1.5 g, 4.63 nunol) and aicotinyl chloride hydrochloride (0.99 g, 5,56 itjmol) in THF (25 inL) was added TEA (2 mL, 13.89 mmol) at 0 0 C and stilted for 20 h at RT. After msual aqueous work-tip and chromatographic purification, 1.0 g (83%) of 1 «CIA»MW>15 was obtained as a yellow viscous liquid, 1 H NMR (CD₃OD, 500 MHz): δ 0.89 (t, 6H, J - 5.0 Hz) J.29MJ3 (ra, SH)₃ 1,64 (bs, 2H), 3 (t, 2H, J = 5.0 Ez), 3.07 (t, 2H_wJ = 5.0 H2), 4.42 (t, 2H_fJ - 5.0 Hz), 4.63 f 2H, J •• 5.0 Hz), 7.41-7.43 (m, IH), 8.31 (bs, IB), 8.78 (bs, IH), 9.26 (s, IH). MSr ES⁺ ra/z 429 [M+Hf, 451[M+Naf, 467 p Λ +Kf.

20 Example 70

Synthesis of mutual prodrug of g-\bapentm cfttyl ester and xwcoljiMc acid (I-CA-MWH8):

To a solution of BOC deprotected I-S12-PD2 (synthesized as described in Scheme \% Method C and thea deprot \(\beta\) ted using a known general d\(\beta\) protectioflt method) (3.76 g, 7.64 mmol) in \(TBf \) (30 mL) \(was \) added nicotinyl chloride hydrochloride (1.5 g, 8.40 \)

25 \(\beta\) imol), followed by TEA (4.26 inL, 30.56 r\(\phi\) nol)) and stkred ove \(\pi\) it at RT. After usual aqueous work-up and chromatographic purification, 0,97 g (23 %) of I-CA-MPD i 8 was obtained as a yellow oil \(\beta\) H NMR (CDCl₃, 300 MHJ): S 1.24 (t, 3% J = 6.0 Hz), U7-1.47 <m, 10H), 2,27 (s. 2H), 2.90-3,17 (m, 4KQ, 3.16 (d, 2H₅J = 6.0 Hz), 3.79 (q, 2H, J = 6.0 Hz), 4JO (q, 2H, J - 6.0 Hz), 4.36 (t, 2H, J\(\beta\) 6.0 Hz), 5.56 (bt, IH, J - 6.0 Hz), 7.32-7.38 (m, IH), 8\(\Lambda\)7(d, IH, J \(\simes 9.0 \) Hz), 8.71 (d, IH, J \(\simes 6.0 \) Hz), 9.07 (\(\delta\) IH). MS: (ES)\(\text{h} \) n/z 484 (M+H)\(\simes \), 506 (M+Na)\(\simes \); (ES)\(\begin{array}{c} \pi\) jn/z 482 (M-H)\(\simes \).

Synthesis of mutual prodrug of levetilacetam and valproic acid (T-CA-MPD19);

To a solution of tevotiracetam (1.0 g_> 5.87 vmo i) in DCE (20mL) and PCM (4mL) was added oxalyl chloride (894 mg» 7.05 ramol) and heated ^t 80 °C for Th. The reaction mixture was cooled to RT, a solution of I-C1-PP11 (1.97 g, 7.05 ramol) in DCE (10mL) was added and stirred at RT for 18 to. Aicr usual aqueous Aorjwip and chromatographic purification, 1.73 g (61 %) of X-CA-MPD19 was obtained as a yellow oil. ¹H NMR (CDC1₃, 300 MHz); 5 0.8S-O.91 (m, 9H), 1.24-1,62 (m, SH), 1.80-2.05 (tn, 4H), 234-2.44 (m, 3H), 2.91 (t, 4H, J * 6.0 Hz), 3.03-3,12 (m, IH), 4.05-4,09 (m, IH), 4.31-4.36 (m_>4H), 8.32 (bs, IH). MS; (ES⁴) m/2 477.1 [M+H| +, 495.9 [M+Naf (ES) " ttt/z 475.0 [M-H].

$E\chi a in \rho)$ (fc72

Synthesis of mutual prodrug of gabapentin ethyl ester $m \dot{\alpha}$ valproic acid (I-CA-MPD21): This mutual prodrug was synthesized by following a route depicted in Scheme 19, with obvious modifications. The mutual prodrug I-CA-MPD21 was obtained as a colorless oil. ¹H-KMR (CDCl₃₃ 300 MHz): 5 0-81 (t_>6H, J = 7 Λ 9 Hz), U5- $\ddot{1}$.60 (in, 21H), 2.20 (s, 2H)₁2.25-2.35 (m, IH), 2.84 (t, 4H, J * 6.6 Hz), 3.11 (d, 2H, J « 6.7 Hz), 4.05 (q, 2H, J = 7 Λ 6 Hz and 17-3 Hz), 4,15 $^{\circ}$.25 (m, 4H), 5.43 (bt, IH). MS (mfz): 506 ps Λ +Hf, 528 [M+Naf.

20 Example 73

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Synthesis of mutual prodrug of gabap β ntm ethyl ester and nicotinic acid (\ddot{I} -CA-MFD22): To a suspension of mcotinyl chloride bjnfcochlOtide (0.35 g» 1.97 mmol) in THF (3 mL) at 0 "C was added TEA (0.82 røL_> 5,91 mmol). Afef 5 imn, a solution of I-A1-PD8 (0.5g, L31 mmol) and TEA (0.27 moL, 1.97 mmol) in THF (4 mL) was added and stirred ovemigbrt at RT. TUe mixture was purified by column chromatography to afford 0.573 g (90 %) of>CA-MP»22 as a yellow oil 1 H NMR (O)Cl $_{3}$, 300 MH φ δ 1.24 (t, 3H $_{7}$ 1 \approx 6.0 Ha), 1.27-1.47 (m, JOH), 2,27 (s $_{2}$ 2H), 2.94 (t, 2H, J - 6.0 BzI 3.07 (t, 2H, J - 6.0 Hz), 3.19 (d, 2H $_{3}$ J * 6.0 Hz), 4.12 (q, 2H, J = 6.0 Hz), 4.32 (t, 2H, J - 6.0 Hz) $_{1}$ 4.62 (t, 2H, J $_{2}$ 6.0 H4 5.29 (bs, IR), 7.36-7.42 (m, IH) $_{1}$ 8.30 f IH, J = 3.0 Hz), 8.78 (dd $_{2}$ IH, J = 1.69 Hz) $_{2}$ 9.24(s, IH)- MS: (ESf m/z 4S5 (M+H)+ $_{3}$ 507 (M+Naf $_{4}$

Exatttjile 74

Synthesis of jauiual prodrug of tennottigine and valproic acid (I-CA-MP3D23): To a suspension of lamottigme $(0.455 \ ^{\circ} \ _{1}1.78 \ \text{irtmol})$ and 0MAP $(0.217 \ \text{g}, 1.78 \ \text{titmol})$ in toluene (IO ml) at $110\ ^{\circ}\text{C}$ was added a solution of the ÚmdazoHde of I-CI-PPII $(0.665\ \text{g}, J,78\ \text{ramo})$ inTHP(5i»L). TJie reaction wsstinsd at $110\ ^{\circ}\text{C}$ overnight and purified by column chromatography to afford 0.20 g (20%) of I-CA-MFD23 as a white solid. ^{1}H NMR (300 MHz, CDCI₃): δ 0.86-Q.90 (m, 6H), 120AM (m, 6H), 1.53-1.62 (m, 2H), 236^29 (tn_1H), 2.90-3.0 (ra, 4H), 4.34 (t, 2H, J = 6.3 Hz), 4,46 (t, 2H J = β £ Hz), 7.36-7.38 (m, 2H), 7.60-7.63 (m, IH). MS: (ES +) m/z 562 (M+Hf $_{5}$ 585 (M+Na)+,

10 Example 75

Synthesis of mutual prodrug of $la\pi\omega$ trigine and nicotinic acid (t-CA-MP))24): A solution of X-AX-FJM (0.5 g, 1.14 mmol) and TEA (0,5 mL, 2.87 rørool) in THF (5

mL) was added to a suspension of nk αinyl cWdride (0,305 g, 1.71 πuno)) and 0.5 mL TEA in THF (5 mL). The mixture was stinted at RT for 24 h. After usual aqueous *vroikr*

up and ckomatographic purilcation, 0.15 g (14%) of Jt-CA-MPDM were obtained as a white solid, 1 HNMR (CDCl $_{3j}$ 500MHz): δ 3.06 (t, 2H, J - 6,5Hz), 3.10 (t, 2& J ° 6.5 Hz% 4.49 (t, 2H, J ° 6.5 Hz), 4.65 (t, 2H $_{1}$ J = 6.5 Hz), 7.38-7.43 (m, 3H), 7.60-7,62 (m, IH), S.33-8.36 (m $_{1}$ IH), 8.81 (m, IH) $_{5}$ 9.35 (b\$ $_{8}$ JH). MS: (ES +) jn/z 540.9 (M+H) $_{1}$ +.

Example 16

Synthesis of mutual j*od Tug of lam Origin ε and nicotinic acid (I-CA-MPDJtS);
This ratttwai prodbig vm synthesized using lamot ήgine axnd nicotiayl chloride hydtxichlorid β, appoording to the methods outlined in Scheme XI and Scheme 17, 0.8 g (44%) of Ï-CA-MPD25 J[CI were obtained as an off white sotfd. ¹H NMR (D₂O, 500MHz).' 5 2.93 (t, 2H, J - 6.5 Ut) 73.10 (t, 2H, J - 6.0Hz), 3.69 & 2H, J = 6.5Hz), 4.49
(in, 2H), 7.37-7,43 (m, 3ÏT), 7.69-7.71 (m, IH), S.P5-S.07 (m, IH), S.78-8.79 (m, IH),

(iii, 2H), 7.37-7.43 (iii, 3H), 7.09-7.71 (iii, 1H), 8.73-8.07 (iii, 1H), 8.76-8.79 (iii, 19.30 6.9 aH) 6.79 (iii, 1H), 6.79-7.71 (iii), 6.79-7

Example 77

Synthesis of mutual prodrug of metronidazole and norfloxacin (I-AH-MPDI):

Step 1: Synthesis of imife>)toe of I-Hl- | *\frac{1}{1} t;

30 CDI (319 mg, 1.97 mmol) was added to a sotøti Ch of I-HX-PDI (577 mg, 1.64 mmol) in DMF (8 1)L) and stirred at RT for 4 K The mixture was concentrated and the residue

purified by column chromatography to give 395 mg (54%) of the imidazolide of **I-HI-PBI.** ¹H-NMR (300 MHz, CDCl₃): δ 2,50 (s, 3H), 2.92 (t₅ 2H₃ J « \$.0 Hz), 3,00-3,10 (m, 2H), 436 (ϵ > 2E J = 3.0 Hz), 4,47-4.51 (ϵ) 34.57-4.70 (ϵ) 446, 7.07 (S₁ IH) 37.43 (s, IH), 7.95 (ϵ) 18, 8.15 (s, IH). MS (ϵ) 446 [M+Hf.

Step 2: Synthesis of 1-AH-MPDI: A solution of die mridazolide of 1-HI-PDI (100 mg> 0,224 mmol) in DMP (1 πiL) was added to a suspension of norfloxacin (86 mg, 0.269 mmol) in DMF (2 mL) and s&ted at RT for 60 h. The πύχτυίε was conccattated and the residue purified by column chromatography to give 35 mg (22%) of I-AH-MPDt ¹H-NMR (300 MHz, CDCl₃); δ 1.59 (t, 3H₁ J = 7.5 Hz), 2.53 (s, 3H), 2.86-2,97 (m, 4H), 3.27-3.30 (fo 4H), 3.72 (t, 4H, J * 4.5 Mz), 4.324.40 (m, GH), 4.48-4.52 (m, 2H), 4.59-4.63 (in, 2H), 6.85 (<3, IH, J - 6.0 B#, 7.96 (s, IH)₁ 8.09 (d, IH₁J = 12.0 Hz)_w S.68 (3, III). MS (m/z): 6\$7 [M+H3+.

The following rout Cai ptottrugs (Examples 78 - 80) -wete obtained actsording to procedure siMlar to Uiose described, in Example 77, with the substitution of the appropriate pairs of amino-coDtaining and hydroxyl-containing therapeutic agents:

Example 78

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Synthesis of mutual prodrug of metronidazole and ttorfloxacin (I-AH-MPP3b): The mutual prodrug I-AH-MPD3b vrøs obtained as a yellow soïid. $^{\rm I}$ H-I $^{\rm A}$ MR (300MHz $^{\rm A}$ CDCI₃); δ 1.59 (t, 3H, J = 7 Λ Hz), 2.49 (s, 3H), 2.82-2.9S (m $^{\rm A}$ 10H), 3.30 (t, AO, J = 4.5

20 jffe), 3.39 (bs_w4H), 3.72 (t_>4H, J = 4,8 Hz), 4J S (dt. 8H₅J $^{\circ}$ 26,2, 6.4 Hz), 4.61 (t, 2H, J * 4.8 Hz), 6.86 (d, 1H, J $^{\circ}$ 6.4 Hz), 7.?5 (s, 1H), S.07 (bd, 1H, J = 12.8 Hz,), 8.67 <s, 1H), 14.9 (B, 1H), MS (m/z): S1 1,26 [M-HH]⁺,

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Synthesis of mutual prodrug of gatop β -tta and tramadol (\ddot{l} -AH-MPD7):

The mutual prodrug vrøs synthesized according to the method in Scheme 17 with obvious modifications. The wiutual prodrug Ï-AH-MPD7 was obtained as a colorless gummy material, ¹H-NMB. (300 MHz, CDCl₃): 6-1.25 (t, 3H, T •» 7,1 Hz), 1.32-2.45 (m, 30H), 2.91-2.?9 (M, 4H), 3.16 (t, 2H, J - 7.3 HK)₅ 3.80 (s, 3H), 4.08-4.15 (q, 2H, J « 7.1 Hz), 4.284.40 (jo, 4R)₁ 5.4 <t, 1H), 6.74*6,81 (to, 3H)₃ 7.23-7.2? (t, 1H, J - 8 Hz). MS (ffl/z): 669.'30 [M+Hf].

Example \$0

Syndesis of mutual prodrug of venlafaxi π e and paroxetine (|« Λ H-MP»8):

The mutual prodrug was synthesized according to the method outlined in Scheme 17 with obvious modifications, The mutual prodrug I-AH-MPD8 -was obtained as a white sticky solid, ¹H-NMR was consistent with the expected structure. MS: m/z 812 [M]⁺.

5 Example 81

Synthesis of NO-feleastttg prodrug of Valproic acid (t-Cl-NOPDI):

TMs prodrug was synthesized as shown in Scheme W, Method B using as reagents valproic acid (725 mg, 5,03 nunol), Ltøb (1 g, 5.03 mmol), TEA (6U mg, 6.04 mmol), DCC (1.25 g, 6.04 moral) and UMAP (10($\lambda m \& Yield: S32 mg (51\%), ^1H-NMR (300 mg))$

10 MHz, CDCl₃): δ 0.89 (t, δ H, J $^{\circ}$ 7.09 Hz), 1.22-1.77 (m_> 8H)₃ 236-2.40 (m, IH), 2.93-3.00 (m, 4H), 4,34 (t, 2H_• J $^{\bullet}$ 6.8 ife), 4.70 (t, 2H₉ J $^{\sim}$ 6.35 Bfe). MS (CQ⁺ ra/a: 326 [M+Hf.

Example 82

Synthesis of NO-i βleasing prodrug of valproic aci4 Of-O-NOPrøa):

- This prcklrug was prepared as shown in Scheme 13, Method A. Thus, to a stilted mixture of valprayl isocya@tate, which was freshly prepared from valpr@mide (0,7 g>4,90 mmol [valjjromide wias synthesized from valproic acid by using known methods as shown in. Scheme 11, Method I) using a known method (se&J. Org. Chem., 1962, 27, 3742) in DCM (20 mi) at RT was added a solution of JLtøb (0.976 g, 4.90 mmol) in DCM (5 mL) drop-wise and sticisd at RT for 2 h. The wiixtate was concentrated and the residue, after usual aqueous work-up and chromatographic purification, afforded 0.6 g (33%) of prodrug I-CI-NOPDSa. H-MMR data b consistent with the expected structure. MS: [ES] *to/z 391[M+Waf >407.2 [M+Kf; (Eq+ mfe 368 [M+H]*.
 - Example 83
- 25 Syntheaig of KO-releasing prodrug of aspirin (J-G1-NOPD4):

This prodrug was synthesized as shown in Scheme 1!, Method D. Thus, to a solution of aspirin (3.0 & 16,65 mmol) in THF (30 $\tan L$) at 0 "C was added oxally chloride (3.86 raL, 21.64 mmol) and heated at 70 "C for 2 K The tnixtøte was concentrated, the K-\$idws was dissolved in 1HF (30 triL) and treated with a solution of LI-Ia (3.61 g, 1&65 mmol),

30 TEA (3.48 πiL, 24,97 ramol) and DMAP (361 *ng) Ia THF (20 mL). The resulting mixture was stiπed at RT for 2 h and filtered through celite. The filtrate was concentrated

and the residue purified by column chromatography to afford 3.06 g (48%) of the tøomide SIMI, 1 H-NMR (300 MHz, CDCl₃): δ 2.35 (s, 3H), 3.01-3.12 (m, 4H), 3.61 (t, 2H, J = 6.5 Hz), 4,53 (t, 2H, J = 6.0 Hz), 7.11 (dd, IH, J - S Hz, 1 Hz), 7.32 (t, ZH, J = 7.6 Hz), 7.57 (t, IH₁J « 1 7.6 Hz)₃ S.03 (dd, IH, J « 7.8 Hz₄ L6 Hε), MS (ES⁺) m/z; 403.92 (MW-

To a solution of SII-II (2.0 g, 5.27 mmoi) in acetomtrile (20 ml) at 0 *C was added-AgNO₃ (1.07 g, 6.32 mmd) in the dark. The mixture was birred at RT for I.5 h, filtered through celite attd concentrated, The residue, after usual aqueous work-up and chromatographic purification, afforded 0,965 g (50%) pure I-CtøSFOHR lH-NMR (300 MHz, CDCl₃): δ 2.36 (s, 3H), 2.98 (t, 2H, J « 6.8 Hz), 3,05 (t, 2H, J = 6.4 Hz), 4.54 (t, 2H₁J - 6.4 Ifo), 4.70 (t, 2B, J = 6.8 Hz), 7.12 <d, IH, 3 « 8 Hz), 7.33 (t, IH, J - 7.6 Hz), 7.59 & IH, J = 7.5 Hz), S.03 (dd, IH₅J = 7.8 Hz₃ 1 Hz). MS (ES)+ m/z: 379,11 (M+NE,) 4, 383,98 (M+Na)+,

Example 84

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15 Synthesis of NO-releasing prodrug of aspirin (I-Cl-NOPHSa):

As shown in Scheme 11, Method H, this prodrug was synthesized f_i tkee steps:

Step 1: To a suspension of aspirin (1 g, 5.55 mmoi) in benzene (15 ml>) mi DMF (1 drop) at 0-5 0 C was added a solution of oxalyl chloride (0.6 mL, 6.66 mmol) in benzene (5 mL) and stirred at 85 0 C for 2 h. The reaction mixture was concentrated, and the crude acid chloride was used immediately in tree next step.

Step 2; To a SOMO Λ of the above acid chloride in benzene (30 mL) was added silver cyanate (998 mg_>6.66 mmol) and refluxed in the dark for 1 fa. The mixture, containing 2-acetoxybenzoyl isocyanate, -was coojfed to RJ and used in the π ejt* step.

Step 3: To the above mixture was added a solution of U •2b (1.33 g, 6.66 mmol) in benzene (5 mL) and stirred at RT for Ih. The inixture was filtered ttøocgh celite and concentrated, and the residue was purified by column chroraatogr-\$\ph\$ hy to afford \2 g (54%) of pure I~Cl-NO0P»5a. \[\frac{1}{1}H-NMR \] data is consistent with the expected Structure. MS (ES"\[\frac{1}{2}\]) ro/z: 404.98 (TW-Hf, 426.94 [M+Haf, 442,97 |M+Rf, (BS\[\frac{1}{2}\]) m/x 403.01 (M-H]-.

30 Example 85

Synthesis of sodium salt of NO-releasing prodrug of aspirin, 0L-Cl-NOH>5b):

To a suspension of 60% sodium hydride (45 mg, 1,3 nimol) in THF (0.5 mL) was added solution of I-CI~NOPD5a (500 mg₃ 1.24 mraol) in THF (1.5 mL). After stirring for 5 min, THF WS removed under vacuum, the residue was washed with dry EtjO (4x 3 mL) to remove unreacted starting material and dried in vacuum to afford 410 mg (78%) of I-CI-NOPX SIJ as an off-white solid, JH NMR (D₂0, 500 MHz): 6 2.28 (s₇ 3H), 2.93-2.97 (m> 4HX 4.33 (t, 2H, J « 6.0 Hs), 4.68 (t, 2H₅ J - 7.2 Hz), 7.07 (d_s IH, J = 8.0 Hz), 7.26 (t, IH, J * 7.5 Hz), 7.41 (t, IH, J • 9.0 Hz), 7.57 (d, IH, J = 7.5 Hz). MS: m/z 427.0 01+H) +, 449.0 DMHNaJ*.

Example #6

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This prodrug TVas syn&estøed as shown in Scheme 11, Method E. Thus, to a solution of aspiria (1.20g, 6.70 aimol) in DCM (15 mL) at 0 °C was added oxalyl chloride (0.74 iriL,

Synthesis of NO-ieleasing prodrug of aspirin Qt-Cl-NOHM):

8.65 Ofmol) and stirted at RT for 1.5 h. The mixture was concentrated and the residual acid chloride was treated with Lt-S-TFA (6.70 mmol) in DCM (14 mL), followed by drop-wise addition of TEA (3.73 mL, 26.81 π røiol) at 0 °C. The ^mixture was sticred at RT for 4 h and concentrated,. The residue, after usual aqueous work-up and chromatographic purification, gave 0,822g (34 %) of \ddot{l} -C1-NOPP6. 1 H-NMR (300 MHz, CDCl₃): δ 2.35

(s, 3H), 2.92 (t, 2H, J = 6.11 Hz), 2.98 (t, 2H, J = 6.0Hz), 3.76 (q, 2H, J \(\cdot \) 6.0 Hz), 4.71 (t, 2H, I = 6.0 Hz), 6.70 (bs, IH). 7-10 (d, IM, If \(\alpha \) 9.0 Hz), 7.31-7.33 (m, IH), 7.48-7.50 (m,

20 IH), 7.78 (d, IH, J β ^ OHz)- MS (EI)⁺ m/z; 361 (M+H)⁺.

Examples?

Synthesis of NO-ieteasing prodrug of nicotinic acid (I-C1-PJOPD7):

This prodrug was synthesized as shown in Scheme 11, Method C. Thus, to a suspension of nicotinyl chloride hydrochloride (2.68 g, 15.07 raraol) in THP (10 mL) at 0 0 C was added a solution of 11-21» (2.0g, 10.05 mmol) and TEA (5.6 $mL_{>}$ 40.2 mmol) in THF (7 mL) and stirred at RT for 15 k The mixture vm filtered, cojteenttaied and the residue purified by column chroro-itogiaphy to afford 2.23 g (73%) of pure I-CH-NOFDT 1 H-NMR (300 MHz, CDCl₃); δ 3,01 (t, 2H, J * 4.75 Hz), 3.09 (t, 2H, J =6.S Hi), 4.63 (t, 2H, J = 5.25 Hz). 4.70 (t, 2H₅ J «4.75 EB), 7.3? - 7,42 (m, IH), S-29-B31 (d.t, IH, J « 8 Hz, 2 Hz)₂ 8.78-8.80 (dd, 1H» J = 2 Hz), 9.23 (d₅ IH, J = 2Ha). MS (ES)+ m/z: 305 (M+H)+.

Synthesis of NO-teleasing prodrug of nicotinamide (MTl-NOPD βa):

Synthesis of NO-releasing prodrug of nicotinic acid (I-Cl-NOPJW):

This prodrug was synthesized as shown ia Scheme 11, Method, F. Thus, TEA (6.92 mL, 50.55 xomol) -was added to a suspension of wcot tayl chloride hydrochloride (3.0 g_> 16.85 ttrørøl) and cysteammebycUocMotide (241 g, 18.53 mmol) in DCM (30 mL) at 0 °C and stirred at RT for 4 h. Tree mixture was concentrated and the residue dissolved in MeOH (20 mL). To this solution at 0 °C was added a solution of LI-3b (4.11 g, 16,85 mmol) in MeOH (5 mL), followed by TEA (4.61 mL, 33JO mmol) and stirred overnight at RT. The mixture "was filtejred through celite, concentrated and the residue was purified by colunwi chromatography to afford 3 g (58%) of pure *C1-NOPD9.

1H-NMR. (300 MHz, DMSO-Ii s); 2.94 (t, 2& J * 6-7 Hz), 3.09 (t, ZH, J - 6.3 Hz), 3.56 (q, 2H> J - 6.3 Hz), 4.73 (t, 2H, J -»6.3 Hz), 7.49-7.53 (m,lH), 8.16-8.19 (m, IH), 8.69-8.70 (m, IH), 8-87 (bt t, IH), 8.98 (s,I]HO. MS (BS¹) m/zt 304 (M+H)+, 326 (M-Wa) +.

Example 90

Synthesis of NO-xelcasmg prodrug of π apfoxe $\alpha(1-Cl-NOl DlO)$:

This prodrug was synthesized as shown ia Scheme 11, Method B. Thus, to a solution of naproxen (2L23 g, 9.7 mmol) and M-2b (1.93 g, 9.7 mmol) b THF (70 mL) at RT were added DCC (3 % 14.55 mmol) and PMAF (1.78 g, 14.55 πanol) and stored oveπὑght. The mixture was filtered and concentrated, and the residue purified by column chromatography to afford 1.03 g (25%) of pwe I-Cl-NOPPIO. ¹H-NMR (300 MHz, CDCl₃); 8 1.59 (d, 3H, J - 7-16 Hz), 2.81 (t, 2H, J - 6.77 Hz), 2.97 % 2H> J = 6.42 Hz), 3,85-3.88 (m, IH) 4 3.91 (s, 3H) 4.33 (t, 2H, J = 5.26 Hz), 4.53 (t, 2H, J * 6.79 Hz)> 7.10-7.16 (m₃2H),7.41 (d, IH₅J ^ 1.7Hz), 7.69 < 3H, J = S.55 Hz).

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Synthesis of NO-releasing prodrug of naproxen (I-Cl-NOP&tø):

This prodrug was synthesized as shown in Scheme U, Method E Ttas, to a solution of naproxen (1.69S g. 7.37 mmol) in chloroform (20 mL) at 0-5 0 C was added ox β tyl chlo π de (0.8 mL, 8.844 ftimol), followed by 2-3 drops of DMF. The mixture was stirred at RT for 90 mitt and concentrated. This acid chloride (~7,37 mmol) was treated with LI-5.TFA (6,7 mmol) \dot{m} TBF (20 mL) and cooled to 0 0 C. To this was added TEA (5.6 mL, 40 mmol) and starred at RT for 3 h. The mixture was concewtrated and the residue, after usual aqueous work-up and chromatographic purification, afforded 0.409 g (14%) of pure $\ddot{\Gamma}$ - α -NOrø>12. 1 H-NMR (CPCl $_{3}$, 300 MHz): δ 1.24 (d, 3H), 2.87 (t, 2H, J = 6.5 Hz), 2.93 (t, 2H, J $^{\circ}$ 6.7 Hz), 3.64 (q, 2H, 7.5 Hz), 3.76 (m, IH), 3,88 (s, 3H), 4J O(t, 2H» J $^{\circ}$ 6.6 Bfc), 4.79 (br s, IH) $_{3}$ 6.97-7,08 (m $_{8}$ 3H), 7-35-7.46 (m. 3H). Example 92

Synthesis of NO-releasi πg prodrug of flurbiprofen (Ï-C1*-NOM>13):

This prodrug was synthesized as *shffvm* in. Scheme U , Method A , using as reagents flurbiprofen (4,0 g, J6-37 π Ünol), CDI (3.97 g, 24.56 ω moi) and LI-2b (325 g, 1637 rømol). Yield; 3 g (43%). ¹H-NMK, (300 MHz, CDCl₃): δ 1.56 (d, 3H, J = 11 Hz), 2.80-3.0 (jn, 4H, J = 5.67 Hz), 3.78 (q, IH, J = 7.10 Hz), 4,36 (m, 2H)» *& (t, 2H_wJ = 6.78),

7.11-7.54 (m, 8H).

Example 93

Synthesis of KO-ielcasing prodrug of fluibipiofen (J-Cl-NOPDWa):

This pxodrog was Syn-hesizfid as shown in Scheme 11, Method I. Ttus, to a solution of flurbiprofen (5.0 g, 20.46 mmol) in benzene (50 mL) was added oxalyl chloride (3.11 g, 24.55 jrattol) at 0 "C aod 2 drops of DMF and stiwed at RT foc 20 his. Beozene was removed raider vacuum and the residue was diluted with DCM (50mL). The reaction mixture was cooled to 0 °C and dry ammoma -was passed for 30 min. The reaction mixture was concentrated aad, after usual aqueous work-up, 4.5 g of flurbiprofen amide was obtained a\$ a white solid.

was cooled b RT and treated with L1-2 \triangleright (2.45 g, 12,33 irøiot) in DCE (10mL) and stirred overnight After usual aqueous work-up and chromatographic purification, 0.5 g of PCI-NOJPJ) Ma were obtained. H NMR (CDCI₃, 300 MHz): 5 1.55 (d, 3H, / = 6.9 Hz), 2.94-2.97 (bs, 4H), 438-4.47 (bs, 3H), 4,68 (t, 2H, J = 6.6 Hz), 7.13-7.55 (bs, 8H) MSi ES+xttfz 469.03[M+Hf, 467.16 IM-H)+.

Example 94

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Synthesis of NO-releasing prodrug of flurbiprofen (I-Cl-NOPDISb):

This prodrug was synthesized as shown in Scheme 11, Method A. Thus, \dot{b} a solution of flurbiprofen (2.5 g, 10.23 ramol) in THF (30 mi.) was added CDI (3.31 g, 20.46 mmol) and stiwed at RT fof 16 h. To tiws was added \ddot{l} 1-S TFA (3.64 g, 10.23 mmol) in THF (15 mL), followed by TEA (2,85 mL, 20.46 ramol) and stirred for 16 h. After usual work-up and et@Otnatogjtaphic purification,, 1.5 g (91%) of 1-Cl-NOPJOISb were obtained. 1 HNMR (CDCI₃, 300 MHz): 8 1.5 (d, 3H $_{>}$ J = 6.9 Hz), 2.82 (t, 2H, J = 63 Hs), 2.92 (t $_{>}$ 2H, J - 6.9 Hz), 3,50 (m, 3H) $_{>}$ 4.6 (t, 2H $_{>}$ J - 6.6 Hz), 5.8 (s, IH), 74 1-7.55 (bs,

1S SH). MS: ES⁺ ra/z 425.21[M+HJ⁺, 423.11 [M-H]*.

Example 95

Synthesis of NO-teleasing prodrug of indomethacin (I-C1-NOPIM6):

ittdomethacin (2.0 & 5.59 πttnol) in chloroform. (25 mi.) was added CDI (1.09 g, 6.71 mmol) and stirred for 2h, A solution of U-2b (1.22 g, 6,15 wonol) and DMAP (751 mg₅ 6.15 mmol) in chloroform {5 mL) was added, and the mixtare was stinted at RT for 16 h. After usual aqueous -woiK-up and chromatographic prøification, 2.02 g (67%) of pure I-CX-NOme was obtained. ¹H-NMR (300 MKs, CDCl₃): S 239 (s_>3H), 2.88-2.95 (m, 4H), 3.69 (s, 2H), ZM (s_>3H), 4.38 (t, 2H, J « 6.3 Hs), 4.63 (t, 2H, J ^ 6.6 Hz), 6.67 (dd,

This prodrug -was synthesized as shewn in Scheme 11, Method A. Thus, to a solution of

2S IH, J = 2.4, 8,7 Hz)₅ 6.87 (d₄ IH₃J - 8.7 Hz), 6.96 (d, IH, J = 2.J Hz), 7.47 (d, 2H, J = 8.4 Hz), 7.67 (d, 2H₂J - 8.4 Hz). MS (ES⁺) m/z; 539.2 m+Hf> 560.79 [M+Na]⁺.

Example %

Synthesis of NO-releasing prod π_{rg} of indomethacin (J-C1-NOPP18);

This prodrug was synthesized as skrøn in Scheme 11, Method A. Thus, to a solution of indomethaci α(3.01 g, 8.42 mmol) in THF (50 mL) at RT was added CDÏ (1.64 g₃ 10JO tmol). After 1 h, II-S.T Ï A (3 g, 8.42 mmol) was added at 0 ⁶C₁ followed by TEΛ (5.9

mL, 42.1 roraol) and DMAP (0.6 g, 4.91 thraol). The reaction mixture was stirrød at RT for 2 d, After usual aqueous work-up and chromatographic purification, 3,16 g (70%) of **!-CI-NOPDIS** were obtained as yellow solid. ¹H WMR (CDCJb, 300 MHz): δ 2,38 (s, 3H), 2.79 (t, 2H, J = 6.3 Hz), 2.56 (% m , J « 6.9 Hz), 3,54 (q, 2H, J « 6.0 Rz), 3.66 δ 2H), 3.83 (s, 3H), 4.61 (t, 2H, J « 6.6 Hz), 6,01 (bs₅ IH)₃ 6.71 (d<3, IH, J « 2.1, 9.0 Hz), 6.9 (dd> 2H, J * 33, 8.1 Ks), 7.49 (d, 2H₅J = 8,4 Hz, 2H), 7.66 (d, ZH, J = 8.4 Hz). MS: ia/z 538.10 [M+H]⁺, 560.1 [M+Naf ,

Example 97

Synthesis of NO-jrøleasiπg prodrug of ketopr ofen (ï-Cl-NOrølS):

This prodrug was syattesized as shown in Scheme 11, Method A according to the method described in Exampte 9% using as leageats ketoprofern (1.27 β, 5 mmol), CDI (L21 g, 7.5 mmol) and IJ-2II> (I g> 5 oarnol). Tield; 0,6 g (51%). ¹H-NMR (300 MHz, CDCl₃): δ 1.55 (d, 3H, J « 7.0 Hz), 2.80-2.95 (m, 4H), 3.82 (q, IH, J - 6.7 Hz), 4.35 (t, 2H, J * 6.1 Hz), 4.64 (t, 2H, J - 6.5 Hz), 7.40-7.85 (m, 9H). MS (ES⁺) m/z; 436.06 (M+H1*,45S,O2[M+Na]⁺.

Example 9\$

Synthesis of NO-rfileasing prodrug of ketoprofen (i-Cl-NOPD20a);

This prodrug was synthesized as aiiown in Scheme 11, Method *I* Thus, to a solution of the amide of ketoprofen (1,78 g, 7 jnmol) in PCE (70 mL) was added Φαsiyl cMoxïdo (1.0 g, 8.4 mmol) at 0 *C and xejtøet ï for 16 h. After cooWvs, to RT, a solution of W-2B (1.4 g, 7 Tnmol) π PCE (10 mL) Avas added and stilted for 20 h. After usual aqueous work-up and chromatographic jnirificatior., 0.6 g (17 %) of I-Cl-NOPItt&a -was obtained as a pale yellow gum. ¹H NMR (CDCl₃, 300 MHz): δ 1.47 (d, 3H, J = 6.96 Hz), 3.00 (bs_>4H), 4.00 (q, IH₅ J = 6.Sl Hz)₅ 4.39 (t, ZB, 3 - 6-21 Hz), 4-68 (bs, 2H), 7.47-7.77 (bs> 9H).

25 MS: ES⁴ m/z 478[M+H]\ 477.1 SIM-H]⁺.

Ex#ï«ple99

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Synthesis of NOreleasmg prodrug of diclofenac (I-CJ,-NOPD22):

This prodrug was synthesized as shown in Scheme 11, Method B_s using as reagents diclofenac (1.0 & 3.378 mmol), **LWb** (0.68 g, 3.37 mmo& DMF (S mL), DCC (0.835 g, 4.054 rom d) and PMAP (0.082 g_> 0.675 mmol). Yield; 0.35 g ($2\frac{1}{2}$ %)- 1 H-NMR (300 MHz, CDCl₃); δ 2.91^3,04 (m, 4H)₅3.85 (s, 2H), 442 (t, 2H, J - 6.6 Hz), 4.72 (t, 2H, J -

 $6.6\,\text{Hz}$), $6.56\,\text{(d}_2\,\text{IH}$, $J=8.1\,\text{Hz}$), $6.82\,\text{(g,IH)}$, $6.94-7.03\,\text{(m, 2H)}$, $7.12-7.27\,\text{(m^H)}$, $7.35\,\text{(d, IH, J- 8.1Hz)}$. MS (ES⁺) ra/z: 476.90 (M+Hf, 498.86 IM+Naf . Example 100

Synthesis of NO-retgasing prodrug of flurbiprofen (I-C1-NOPD26):

S Ms prodrug was synthesized as outlined! in Scheme 20. Thus, to a solution of \$20-11 (0,8 g, 2.90 mmol) in THF (10 mL) and DMF (10 mL) was added the cesium salt of flurbiprofen (1,2 g, 3.19 mπnol) and \$tiwed at RT for 2 h. After usual aqueous work-up and ctøomatographic purification, 1,13 g (80 %) of I-Cl-NOPD2 S was obtained as a light yellow seø solid. H NMR (500 MHz, CDCl₃); \$ 1.58 (α, 3& J - 7.5 Hz), 2.88-10 2.94 (m, 4H), 3.88 (q, IH, J= 7.0 Hz)₁4.40 (t, 2H, J= 6.5 Hz), 4.64-4.6S (m, 4H), 7.14₄₄ 7.54 (tn» SH). MS: rafeSOU ÜM+NBU]*, 506.1 βMW Ïaf.

E^mple 101

J5

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Synthesis of NO-r deas Ing prodrug of gab- \phi e \times tijn ethyl ester (I-A1-NOPD1);

This prodrug was synthesized as shown in Scheme 12, Method A. Thus, to a stirred solution of diphosgetie (0.88 mL, 7,37 mmol) in DCM (3 mL) at 0 ⁰C was added dropwise a solution of LI-2a (0.80 g, 3.68 mmol) ss. Hunig's base (1.92 xnL, 11.85 mmoi) in DCM (1 mL). The nuxtate was stiired at 0 ⁰C fbi 30 mb, and ccmcβntmted. The residue was dissolved in DCM (4 mL) and treated with gabapeπin cibyl ester hydrochloride (0.95 g, 4,05 mmol) & Hunig's bass (139 nil, 8.05 mmol). The mixtob was stitred at RT for 3 h aad concentrated. The residue, after usuaï aqueous work-up, gave 1.6 g (98 %) of tSn- ïl. ¹H-I^MR-daia is αmsïstent wüh the expected structare. MS (ES⁺) mfe 444 [M+H]*. 465.9 {TM+Naf.

To a stood solution of I-S12-IX (13 g, 2.94 mmol) in $aeeto\pi trile$ (S mL) at RT was added silver nitrate (0.6 & 3.52 awnol) pottion-wise and stmed at BT for 2.5 h. After filtration through celite, the filtrate was concentrated and the residue purified by coluro α chromatography b afford 0.561 g (45 %) of prodrug I-Al-NOP \ddot{l} M. l H-NMR data is consistent with the expected steucture. MS (ES⁺) toJz: 425 (MfH)*, 447 (M+Na)*.

Example X02

Synthesis of NO-releasing produg of Jataotrigiae (ï-Al-NOPD3a and X-Al-NOFD3b):

This prodrug was synthesized as shtwn *m* Sterne 12, Method B. Thus, to a suspension of lamotagiue (1 g, 3.90 mmol) in toluene (20 mL) at 120 °C was added dtop-wise a.

solution of the imidazolide of *LbIb* (1.4 g, 4.70 mmol) in THF (10 jtnL) and refluxed for 6 h. After usual aqueous work-up and chromatographic purification, 340 mg (20%) of I-AI-NOPD-3a/b was obtained. ¹H-NMR data is consistent with ϕ e expected structure. MS (ES)⁺ π te: 481 (M+H)*.

5 Example 103

Synthesis of NO-releasing prodrug of nicotinic hywazide (Ï-A1-NOPD4):

TMa prodrug was synthesized jfrom nicotinic hydrate (235 mg, 1.70 jnmol) according to the procedure described in Example 109 (see Scheme 13, Method B). After usual workup, the crude product was purified *by* column chromatography to aflbrd 0.21 g

10 (34%) of prodrug \ddot{I} -A1-NOFD4. 1 H-NMR (300 MHz, DMSO-d*): S 3.02 (t, 2 H₁J = 5.8 Hz), 3.10 (V 2H, J - 6.1 Hz), 4.28 (t, 2H, J - 5.8 Bz), 4,76 (t, 2H, J = 6.1 Hz), 7.5 J-7.S5 (dd; IH, J $^{\circ}$ 4.8 $\ddot{B}z$ ₁7.7 Hz)₅8,17 (d, IH, J = 7J Hz), 8.74 (d, IH₅J * 3.8 Hz), SSB (s, IH), 9.44 (bs, IH)₃ 10,54 (fas, IH). MS (Er)Vz: 363 [M+Hf.

Example 104

Synthesis of NO-releasing prodrug of BsiOojpril dimethy] ester (I-A1-NOPDS):

This prodrug "was synthesized from Jisinopril dimethyl cst«r hydrochloride (1.10 g_w 2.56 jmmOI) according to the procedure described in Example 101 (see Scheme 12, Method B).

After usual workup, the crude product was purified by column chromatography to afford 0,76 g (67%) of prodrug Ï-A1-NOH>5.

H-NMR (300 MH*, CDCl₃): S 1.49-1.54 (m, 2H), 1.93-2.07 (m, BH), 2.12-2.2S (m, IH), 2.64-2.68 (m, 2H), 2.91-3,0 (xn, 4B), 3,18-3,25 (m, 3H), 3,42,3,47 (m, IHK 3,52,3,55 (m, 2H), 3,69 (s, 3H), 3,73 (s, 3H), 4,28 (t, II), 3,73 (s, 3H), 4,

3.25 (m, 3H), 3,42-3.47 (m, IHK 3.52-3.55 (m, 2H), 3.69 (s, 3H), 3,73 (s, 3H), 4.28 (t, J ~ 63 Hx, 2H)_S4.47-5.05 (m, IH)₅469 (t, J * 6.8 H^ ZH), 5.22 (bt, IH), 7.14-7.19 (m, 3H), 7.23-7.28 (m_s 2H). MS (EI)Wz: 659 (M+Hf .

Example 105

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25 Synthesis of NO-releasing prodrug of omeprazole (I-Al-NOPM):

This prodrug was synthesized as shown in Scheme 12, Method B. To an ice-cold solution of diphosgenc (0,3 mL, 2.48 mmol) th toluene at 0 0 C, was added a mixture of U-Ob (0.5 g, 2,51 røraol) and TCA (0.42 mL, 3.0 jnmol) io toluene (3 mL) and stirred for ZK U a separate flask, omeprazole (0.867 g, 2.50 mndK) was dissolved in THF (5 mL), cooled b 0 0 C and NaH (0.059 g, 2.5 mmol) was added. The mixture was stirred for 30 min, the above reaction mixture was added dtopwise b it anti stirred for 2 h. After usual aqueous

work-up and chromatographic purification, 0.23 g (20 %) of \ddot{i} -A1-NOPD6 was obtained as a teddish-yellow gum. MS: ES+ $r \phi/z$ 571 (M*H)⁺, 593 (M+Na)⁴:

Ixumpte 106

Synthesis of NO-releasing prodrug of hydralazine (I-Al-NOPDT):

This prodrug was synthesized from hydralazine hydrochloride (0.99g, 5,0 i mmo i) according to the procedure described in Example 109 (see Scheme 13, Method B). Aftesjt usual workup, the exude product was purified by column chromatography to afford 0.8 g (41%) of prodrug I-A1-NOPP7. H-NMR (300 MHz, CDCl₃): δ2.95-3.06 (m, 4H), 4.43 (t, 2H, J = 6,35Hz)₃4.69 (t, 2H₃J « 6.7 Hz)₅7.57 (m, IH), 7,63-7.71(πi, 2H), 8.16 (s, IH),

10 8.29 <d, IH, \ddot{i} - 7,6 Hz). MS (ES⁴) Wz: 386.05 (M+Hf.

Example 107

Synthesis of NO-releasi π g prodrug of amlod ipine (I-A1-NOED8):

Thus prodrug was synthesized from amlodipine (1.67 g, 4.09 rømol) according to the iwocedure described in Example 109 (see Scheme 12» Method B)- After usual workup, the crude product was purified by *colxam* chromatography b afford 1.33 g (6t%) of I-

AX-NOFDJJ. 1 H-NMR (300 *UBz*, CDCl₃); δ 1.18 (t_{8} 3B_>J * 7.1 Hz), 2.36 (s_{9} 3W), 2.93
2.99 (m, 4H), 3.47 (bs, 2H), 3.61-3.64 (m, 5H), 4.04 (q, 2H, J = 7.1 Hz), 4.35 (W, 2H), 4.68-4.74 (rø₉4H), 5.0 (bg₉ $^{\circ}$ BQ, 7.13-736 (m, 4H). MS (ES+) ia/z: 634.14 (M+H)*, 656.83 (MC+Na)*; (BS") m/ $^{\circ}$ K 63L94 OM-H)⁺.

20 Example 108

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Synthesis of NO-releasing prodrug of levetiracetam (I-A2-NOFTOa):

TMs prodrug was synthesized from lewettracetam (1.0 g, 5.87 mmol) accoïding to the procedure generally described in Example 82 (see Scheme 13, Metiiod A). After usual workup and chromatographic pittification, the product *was* further purified by preparative HPLC to afford 728 mg (31%) of prodrug I-A2-NOW>la. IH->MR was consistent -with

the expected structure MS (BS\^ rote 396,1 [M+Hf, 418.1 {M+Naf, (ES)}" mlz: 394.1 [M-H].

Example 109

Syndesis of NO-releasing prodrug of valdecoxib (Ï-A3-KOPD Ja):

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This prodrug was synthesized as shown in Scheme 13, Method B. Thus, to a cold suspenstøi of sodium hydride (271 mg, 6.81 iranol) in TOF (7 mL) was added drop wise a solution of valdecoxib (1J 8 g, 5.68 fflmol) in THF (15 mL) and stirred at RT for Zh A solution of ihe haidazolide of $U\sim2b$ (2,0 g, 6.81 mmol) in THF (15 n»L) was added and stirred at room temperature for Uf The reaction mixture was eonceatrated and the fesidue, after usual aqueous work-up and chromatographic purification, afforded 976 mg (32 %) of prodrug I-A3-NOPDIa. IH-NMR data is consistent with the expected structure. MS (ES)-rø/z; 538 [M-H] ".

Example UO

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10 Syathesis of NO-Wleasing prodrug of celecoxib (I-A3-NOHK.a):

This prodrug was synthesized from celecoxib (6.62 g, 17,35 mmol) according to the procedure described *in* Example 109 (sea Scheme 13, Metfcod B). After usual workup, tibic crude product was purified by column chromatography to affoid 1.55 g (15%) of prodrug **I-A3-NOPI»** a. **1H-NMR** (30Q MHz, **CDCI₃**): 5 2.38 (s, 3H), 184-2.98 (m_>4H),

15 434 f 2H, J •• 6.45 Bz% 4.63-4.71 (ra, 2H), 6-74 (s, IH), 7,09-7.25 (m, 4 H), 7.51 (d_> 2H, J - 6.8 Hz), 8.02 (d_r 2H, J - 6.8 Hz). MS (ES)+ rate 606.87 [M + H]*, 628.73 [M + Naf; (ES)" mfr-604.S8 IM-H] '.

Ex/mplelll

Synthesis of NO-retea\$ing prodrug of paracetamol (I-HX-NOPD1):

This prodrug was sjrathcsized as shown in Scheme 14, Method B. Thus, to a sotution of paracetamol (2.0 g, 13.24 mmol) itt THF (20 mL) was added CDI (2.36 g_> 14.57 romol) and ihe mixture was stirred at RT for 3 h. To this was added a solution of LI-2b (1.21 & 6.62 mmol), followed by DMAP (0.802 g, 6.622 rømol) and stined overnight at RT. The mixture NVas quenched with -water and esteacted with EtOAc. After usual aqueous work-up and chromatographic purification, 0.3 %(6%) of prodrug I-HI-NOPDI 1H-NMR data is consistent with the expected structure, MS (CI)+ raft: 376 [M+111*.

Example 112

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Synthesis of NO-releasing prodrug of paracetamol (L-HI-NOMWa):

This prodrug was synthesized as shown in Scheme IA, Method D. Thus, b a solution of chlorocarbonyl jsocyaaate (0.701 g, 6.622 mmol) in benzene (S mL) at 0 °C was added a solution of paracetatnol (1 g, 6.622 n&raol) and sti π ed at 0 °C for 1 h. To this "was added a

solution of t 1°2b (1.21 g, 6.622 mmol) and TEA (1 mL) in THF (5 mL), and stirred overnight at RT. After usual aqueous work-up axia chromatographic purification, 90 mg (3%) of prodrug I-HI-NOPMa was obtained. H-NMR data was consistent mtk the expected structure. MS: (ES)' mte 418 IM-H)*.

5 Example 113

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Synthesis of NO-releasi π g prodrug of paracetamol (\ddot{l} -H1-NOP03)!

This prodrug was synthesized from paracetamol (2.0 g, 13,24 mmol) according to the procedure described in Example J14 (see Scheme 14, Method C). After usual workup. the crude product was purified by \mathbf{COhxm} ctøomatograjj iiy \mathbf{b} affotd 1.0 g (20%) of piodrog \mathbf{Mil} -NOPD3. H-NJVIR (500 MHz 5 CDCl 3): δ 2.11 (s, 3H), 2.91 (t, 2H, J = 6.5 Hz), 3.06 (t, 2H, J \(\times \) 6.5 Hz), 3.49 (t, 2H, J = 6.5 Ez% 4.75 (t, 2H, J - 6.5 Hz), 7.05 (d, 2H_z J \(\times \) 9.0 Hz)₅ 7.54 (4 2H₅ J - 9.0 Hz). MS (ES)+ mfe 376 tM+Hl +, 393 [M\(\text{offlt}\) \(\text{offlt}\) 397 [M+Kf.

Example H 4

15 Synthesis of NO-releasing produng of metronidazole (TMM-NOPD6):

This prodrug was synthesized in two steps as shown in Scheme 14, Method C.

20 data was rotisisteatwith the expected structure. MS (ES) 4 m/z: 266 Λ [WL+H 4

Step 2: To a n-ixtuiet of UrSTEA. (2.68 mmol) and TEA (t.08 g, 10.72 vm > i) in DCM (10 tnL) at 0 °C was added the ijnidazolide of metronidazole (0,78 g, 2-95 mmol) and swied at RT for 48 h, The reactioxx mixture was quenched with water srod extracted with DCM. After usual aqueous work-up and chromatographic purification 50 nag (4.3%) of

25 \ddot{I} -H1-NOPD6 was obtained. 1 H-NMR (SOO MHz, CDCl₃): 5 2.50 (s, 3H), 2.80 (t_>2H, J = 6.3 Hz), 2.96 (t_>2H, J * 6.6Hz), 3.47-3.50 (m, 2H), 4.4 J (t_?2H, J = S.IHz), 4.58 (t, 2H, J * 5.1Hz), 4.70 (t, 2H, J = 6.6Ha), 7-?6 (s, IH). MS (ES) + mte 395.99 [M+Bf].

Example 115

Synthesis of NO-r $\beta \beta$ asi»g prodrug of bwdesoni'de (I-H1-NOPD9):

30 This prodrug was synthesized & om budeson $\ddot{u}l\beta$ (0.5 g, l.W iffinol) according to the procedure descjibedl in Example 122 (see Scheme 14, Method C). After usual workup,

the crude product was purified by cotøina chromatography to afford 0.25 g (33%) of prodrug 1-H(1-IVOPD?. ¹H-NMR data was consistent with &c expected structure. MS (ES)⁺ Wz: 655 (M+Hf,

Example 116

5 Synthesis of NO-releasing prodrug of 4°Hyd2oxy-TEMPO (t-HX-NO£D10):

A solution of LI-2b (0.20 % 1.20 mmol) and CDI (0.195 g_> 1.20 mmol) in chlorofottn (5 mL) was stirred at RT for 2 ft, which was followed by the addition of 4-hydroxy-TEMPO (0.173 g, 1.00 π unol) and DMAP (0.122 g, 1.00 mmol). The mixture was iefiuxed for 2 ds then purified by column chromatography to afforf 110 mg (27 %) of I-H1-NOPD10 as a red oil. MS: EI+ m!z 398 JM+Hf, 420 [M+Naf.

Example 117

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Synthesis of NO-releasing prodrug of edaravo $\pi\beta$ (1-HI-NOPJ)II):

To a solution of edaravone (0.87 g, 5 mmoi) *in* acontonitrilβ was added KF-Afeθ₃ (66 g) and, tinder thorough mixing, LI-θa (2.8 g, 10 jnmol) was added. The wiixtrøe was agitated for 20 h. After usual aqueous work-up and chromatographic purification, 70 mg (4%) of the iateranediate tøomide 'Was obtained as a reddish-yβllow oil ¹H NMR (CDCl₃, 500 MHz); δ2.28 (s, 3H), 3.00-3.10 (tn, 4H), 3.59 (t, 2H, J = S Hz), 4.34 (t, 2H_S J - 6.5 Hz% 5.S (s, IH), 7.4 (t, 2H, J = 1 Hz). 7.69 (% 3H, J = 1 HK). MS: ES+ J»/Z 375 [M+Kf, 397,0 [M+Na]^.

To a solution of the above bromide (0.05 g, 0.134 mmol) in acetonittitei (1.5 π &) was added AgH0 $_3$ (0.027 g, 0.160 inraol) m $\dot{\alpha}$ sticced for 20 k. After usual aqueous workup and purification 0.025 g (53 %) of **I-Hi-NOPDII** was obtained as a brown gum. ¹H NMR (CDCl₃, 500 MHz); δ 2.28 (s₂ 3H), 2.90 (t, 2H, J = 6.5 Hs), 3.10 f 2H₃ J = 6.5 Hz), 4.33 (t, 2H, S = 6.0 Hz), 4.63 (t, 2H, S = 6.5 Hz), 5.5 (s, IH), 7.60-7.63 (bs, 2H),

25 7.65-7.67 (bs, 3H). MS; ES* m/z 356 [M+Kf].

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Biological Example 1:

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Screening of prodrugs aød mutual prodrugs of antjconynlssntø

Most of the prodrugs and mutual prodrugs of anticonvulsants described In, Ms i β vention were evaluated at National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Health (NIH), wider their Aatjepjleptic Screening Program (ASP).

Test I is an initial screening for anticonvulsant activity in the Maximal Ekctroshodt Test (MES) and Subcutaneous Metøazol Seizure Threshold Test (scMET) models combined with an initial assessment of toxicity (TOX) in mice via Ip. injection (see further explanatioiib $\Theta \omega w$). The data for each condition is presented as N/F, where N number of animals protected from seizure and F = number of animals tested. For test of toxicity, N = number of annuals displaying toxic effects and F = number of animals tested. Any deaths occurring during the test were recorded.

Maximal JEIectπwhock Test (MES); The MES is a model for generalized tonic-clonic seizure and provides an indication of a compound[^] ability to prevent seizure spread wheΛall neuronal circuits in the brain ate maximally active. These seizures ate highly reproducible and elβctro[^]physiologically consistent -with human seizures. For all tests based on MES convulsions, 60 Rz of alternating current (50 «iA in mice) is delivered for 2s by corneal electrodes, which have been primed -with an electrolyte solution containing an anes&etic agent (0.5% tetracaine hydrochloride). Mice were tested at vatraus intervals following doses of 30, 100 and 300 mg/kg of test compound given by i,p, injection of a volume of 0.01 oiL/g. Other doses can be used if indicated by previously known pharmacology. An animal is considered "protected" from MES-induced seizures upon abolition of the hind-limb tonic extensor component of the seizure.

Subcutaneous Metn»zol Seizure Threshold Test (scMET): Subcutaneous injection of the convulsant metrazol produces clonic seizures in laboratory animals. The scMET test detects the ability of the test compound to raise the seizure threshold of an animal and Δ ras protect it from exHb iti π g a clonic seizure. Animals were pretreat β d with various doses of the test compound given by Ip. injection. At the previously determined

Time to Peak Effect (TPE) of the test compound, the dose of metrazol which will produce convulsions in 97% of animals (CD₉₇: 85 rag/kg in mice) was injected into a loose fold of skin in the midline of the necL. The animals were placed in isolation cages to minimize stress and observed for the next 30 minutes for the presence or absence of a seizure. An episode of clonic spasms, approximately 305 seconds, of the fore and/or hind limbs, jaws, or vibrissas is taken as the end point. Animals which do not meet this criterion were considered protected.

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Acute Toxicity - Minimal Motor Impairment (MMI): To assess a compound's undesirable side effects (toxicity), animals -were monitored for overt signs of impaired neurological or muscular function,. In mice, the rotorodl procedure is used to disclose minimal muscular or neurological impairment. When a mouse is placed on a rod that rotates at a speed of 6 rpm, the animal cam maintain its equilibrium for long periods of time. The compound is considered toxic if the animal MIs off this rotating trod three times during a 1-min period. In addition to MMI₇ animals may exhibit a circular or zigzag gait, abnormal body posture and spread of the legs, tremors, hyperactivity, lack of exploratory behavior, somnoten.ee_> stupor, catalepsy, loss of placing response and changes in muscle tone.

Compounds that were active in Test 1 (mice Lp.) were farther screened in Test 2 (rat p.o.). Compounds i^aining actHty in Test 2 (rat p.o.) were selected for secondary evaluation (i.e., Test 3, Rat P.O. quantitation) as explained below

Secondary Evaluations All quantitative *in vivo* anticonvulsani/toxicity evaluations of the active compounds were conducted at compound's time of peak phatmacodyuamic activity (TPE). Groups of at least 8 rats received various doses of the candidate compound until at least two points were established between the limits of 100 percent protection or toxicity and zero percent protection or minimal toxicity. The 95 percent confidence limits, slopes of the regression lines and standard errors of the slopes were calculated fox each quantitative determmation. Rats received test compounds orally.

Test 1 screening results are presented in Table 1, Compound I-CA-MPB24 was active in both MES and scMET mo<iels and was shown to be aoft-toxic. However* some compounds were active in both MES and scMET models and -were also shown to be

toxic The compounds (Le,, I-A1~PD4>I-AA-MPD12, 1-CA-MPD23, I-A1-PD5, X-Al-NOPD3, I-CA-MPD24, I-A1-PD15, Ï-CA-MPD25, and I-AA-MPD11) that are shown to be active in MES but showed no or mild toxicity were selected for Test 2 screening and those results are presented in Table 2.

Three of the compounds (i.e., Ï-A1-PD4, 1-AA-MPP Ï2, and Ï-A1-NOFD3) were considered for secondary evaluation, where quantification of their antiepileptic activity and neurotoxicity in rats (p.o.) was carried out This secondary evaluation determines the time to peak effect (TPE), neurotoxicity, median effective dose (EDso) and biological response. The 95% confidence interval, the slope of the regression line, and Uae standard error are then-calculated, The results of secondary evaluation (Test 3) axe pxesented in. Tables 3A and 3B.

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Table 1: Primary Screening (Test 1) data for Anticonvulsant Activity and Neurotoxicity in Mice (te\$t compound administered Lp.)

Compd	MES ²⁴⁵		ScMET ^{4,c}		Rotorod Toxicity ^{a,d}	
	0.5 h	4.0 h	0.5 h	4.0 h	0.5 h	4.0 h
I-A1-PD7	+(1/1)	-	+(1/1)*	_	+ (2/4) ^d	-
I-A1-PD8	++ (2/3)	-	_	pan .	-	-
	+(1/1)	+(1/1)	+(1/1)	-	+ (4/4) ^f	-
I-A1-PD4	-	+++ (1/1)	-	-		-
	++ (1/7)	++ (3/3)	-	-	-	-
	+ (2/5)	+(1/1)	_	-	-	-
I-AA-	_	++ (3/3)		-	-	-
MPD12	nd	++ (1/3) ²	nd	nd	nd	nd
	-	+(1/1)	-	-	-	
I-CA-		++ (1/3)h	-	-	-	-
MPD23	-	+ (1/3)	-	-	-	_
I-A1-PD13	+(1/1)		+ (1/1)	-	+ (1/4)	-
I-AI-PD5	+(1/1)	-	+ (3/5)	-	+ (3/4)1	-
1-A1-PD6	+(1/1)	-	+ (1/1)	-	+ (4/4)1	
I-A1-PD10	+	-		-	++ (8/8)	nd

I-AA-	-	_	+0/1)		+ (4/4)»	Γ-
MPP13			,			'
I-A ï -NOPDI	++	-	-	-	-	
	(1/3) ^k	-	+(3/1)	-	+ (4/4) ^f	-
	+(1/1)					
I-A1-NOPD3	_	++(1/3)	++	_	+++(1/4)	-
	-	+ (M)	çm 1	_	_	-
'		j	-			
1-CA-	-	++(3/3)	_	-	-	-
MPD24	-	++(3/3) h	-	-	-	-
	-	-H-	-	+	-	-
		(3/3) ^m		(3/1)'		
Ï-A1-PD15	+	++(2/3)		-	-	
	(1/1)	+ (1/1)	-	-	-	-
	~					
I-GA-	+	++(2/3)	-	-	•	-
MPD25	(1/1)	+ (1/I)	-	-	-	-
	-					
I-AA-	-	++(3/3)	-	-	-	-
MPDU	+ (1/1)	+0Λ)	_	-	+(1/4)	-

- aKey; +++ ~ activity or toxicity at 30 mg/kg, ++ · actmly or toxicity at 100 mg/kg >+

 * activity or toxicity at 300 rag/kg, · no activity or no toxicity at 300 mg/3cg
 ^Maximal electroshock seizure test Subcutaneous pentyleaetctrazole seizure test

 dNetw)Jogical toxicity (ntunber of animals exhibiting toxicity/aumber of animals tested).

 e(nttoiber of animal ptotected/number of aaiinal tested), πd M not determined

 fLo3s of rigl Ung reflux. sAt 6 hotiis after dosing. hAt 2 hours after dosing- *Unabte to gmsp røtorod. *Death. kAt 0.25 hours aftex dosing. ^Myoclonic jwfcs. "At 6 Boms after dosittg.
- 10 Table 2: Scteening (Test 2) data for Anticonvulsant Activity aftd Neurotoxicity in Rats (test compound administered p.o.)

Compd	Dose (mg/kg)	Time (h)	MES*,b	Toxicity ^{c,a}
I-A1-	30	0.50	0/4	0/4
PD4		1.00	1/4	0/4
		2.00	3/4	0/4
	}	4.00	4/4	0/4
I-AA-	30	0.50	0/4	0/4
MPD12		1.00	0/4	0/4
	1	2.00	1/4	0/4
		4.00	3/4	0/4
I-CA-	150	2.00	4/4	0/4
MPD23		4.00	4/4	0/4
		6.00	4/4	0/4
		8.00	4/4	0/4
I-A1-	50	0.50	0/4	0/4
PD5		1.00	0/4	0/4
]	2.00	1/4	0/4
		4.00	1/4	0/4
I-A1-	30	0.50	0/4	0/4
NOPD3		1.00	2/4	0/4
		2.00	1/4	0/4
	'	4.00	4/4	0/4
I-CA-	30	0.50	0/4	0/4
MPD24		1.00	2/4	0/4
		2.00	3/4	0/4
		4.00	4/4	0/4
I-A1-	30	0.50	0/4	0/4
PD15		1.00	1/4	0/4
		2.00	3/4	0/4
		4.00	4/4	0/4
I-CA-	30	0,50	0/4	0/4
MPD25		1.00	3/4	0/4

		2.00	4/4	0/4
	ĺ	4,00	2/4	0/4
I-AA-	30	0.50	0/4	0/4
MPDII		1.00	. 2/4	0/4
		100	1/4	0/4
}		4.00	4/4	0/4

^Maximal clecttoshock seizure test, ^(number of animal protected/nuffiber of animal tested). 'Neurological toxicity, d(jbm/T)>foer of animals ejtb libiting toxicity 0A, atoxia)/number of animals tested).

5 Table 3Ai Screening (Test 3) data for Anticonvulsant Activity (Time to Peak Effect) and Neurotoxicity in, Rats (test compound administered p.o.)

Compd	Dose	Time	Time to Po	eak Effect	Toxicity 0*6
	(mg/kg)	(h)	MES 8.0	ScMET" c	(mg/kg)
				(50 mSHSg)	
I-Al-	10	4.0	4/4		
PD4		6.0	3/4		Ì
		8.0	2/4		
		24	0/4		
	30	0.25	2/4	1/4'	0/4 (100)
		0.5	2/4	0/4	0/4 (100)
		1,0	2/4	2/4	0/4 (100)
	•	2.0	2/4	1/4*	0/4(100)
		4.0	4/4	0/4	
I-AA-	15	6.0	2/4		
MPD12		8.0	1/4	<u></u>	

	30	0.5	0/4		
{	ļ	1.0	0/4	1/4	0/4 (50)
		2.0	1/4	0/4	0/4 (50)
		4.0	3/4	0/4	0/4 (50)
		6.0	4/4	1/4	0/4 (50)
)	8.0	4/4	2/4	0/4 (50)
		24	2/4	0/4	0/4 (50)
		8.0			1/8 (100) ^h
I-A1-	30	0.25			0/8 (500)
NOPD3		0.5			0/8 (500)
		1.0		<u> </u>	0/8 (500)
ļ		2.0	1/4	0/4	0/8 (500)
1 1		4.0	3/4	0/4	0/8 (500)
		6.0	3/4	1/4	1/8 (500)
		8.0	4/4	3/4	0/8 (500)
		24	3/4	1/4	

aMaχimal eledroshock seizure teat- "(number of amtnal protected/number of animal tested). Subcutaneous peotylenetetrazole seizure test. ""Neurological toxicity, '(sunibet of animals exhibiting toxicity (i.e., atoxia)/number of animals tested), i teafh following continuous seizure "Popcorn effect and cotttiouons seizure activity. "MUd ataxia only.

Table 3B: Screening (Test 3) data for Anticonvulsant Activity (ED50 and Biological Response and ED5₀) in Rats (test compound administered ρ .o»)

Compd		E	D 50 Values	and Biologi	ical Response	
	Tim c (h)	Dose (mg/kg)	MES46	ED ₅₀	95% Confidence Interval Low/High	Slope/Std.Ex

I-A1-	4	1.9	0/8	T		
PD4	İ	3.8	4/8			
		7.5	4/8	6.55	3.56/10.72	2.27/0.63
		15	7/8			
		30	7/8			
I-AA-	6	7.5	0/8	 		
MPD12		15	5/8	17.1	9.98/25.8	3.2/0.95
	1 .	30	7/8			
	1	60	7/8)	}	
I-AI-	8	3.8	3/8	 		
NOPD3		7.5	3/8			
		15	4/8	10.1	2.99/17/44	1.61/3.15
		30	9/12	1		
		60	8/8		,	

^aMaximal efectroshocfe; seizure test . ^number of atwinalp-Otectied/number of animal tested).

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I-AA-MPP12 is a mutual prodrug of lamotcüginø and gabapetrtin ethyl ester. For this compound, ED₅₀ for the MES model was found to be 17 mg/fcg and the time to peak effect was found to be 6.0-B.Q h at a dose of 30 mg/kg and indicated a significant extension protection (2 out of 4 'animals were still protected) at 24 h after drug administration. Surprisingly, tfiis compound, although less potent than lamotrigine, has exhibited significant extension in the duration of protection. At 50 tng/kg₂ none of the animals exhibited toxicity. However, at 100 mg/Kg, one of eight animals exhibited ttiild ataxia.

I-A1-N0PD3 is a NOreleasing prodrug of lamotrigi π e. For this prodrug, ED50 for the MES model was determined to be 10.1 mg/fcg and the time to peak effect was found be at S.O h at a dose of 30 mg/kg and revealed a significant extension, of protection (3 out 4 animals were still protected) even at 24 h after drug administration. Surprisingly, this prodrug, although less poteat than its parent drug, has exhibited significant extension in the duration of protection. At 50 mg/kg, this compound has also exhibited significant protection (3 out of 4 animals were protected at 8 h after drug administration) in scMET rat model. For the toxicity analysis, only one in eight animals exhibited toxicity at 6.0 h time point at a dose of 500 jng/kg. At other time points (ie., 0.25 b, 0.5 h; 1.0 h, 2.0 h, 4.0 h, 8.0 h after drug administration), none of the animals (0/8) exhibited any significant toxicity at the high dose of 500 mg/kg.

Biological Example %

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The pharmacological experiments on NO-releasing aspirin prodrugs were earned out by following the procedures described herein:

1S Animals and Procedures:

Male or female Sprsgue-Dawley rats weighing 150-200 g were used in the study. The rats were fed normal standard laboratory chow and maintained under standard conditions (room teraperatuie of 22 &2 'C; 50 ± 10 % relative humidity; artificial light 06:00 to 18:00). AH ej ϕ ejriratental procedures mentioned below are approved by institutional aownal research committees and were performed 'in accordance with standard guidelines for the treatment of animals.

Sample preparation and Standard curve;

HPLC: Waters Allience analytical HPLC equipped with 2996 PDA detector and Empower software were used to analyze the samples.

25 HPLC Column: Waters X-T<ara RP-18 analytical column, 150 X 3.9 mm, 5 μ. HPLC Method; How; 1 tnt/mitt, detecter set at 210 ran and at Maxplot (210-400 nm range). Solvent A: Acetonitrile; Solvent B: 0.1% TFA in water, Elution method: A linear gradient of 0-100% A.

Plasma samples were processed by transferring 75 μ l quantity of blood into a test tube containing 250 μ l acetonitrile, vortex-mixed and ceatifiiged at 1000 g for 5 $\pi\dot{\omega}$ i.

the sample was injected into HPLC for analysis. Salicylate standard curves were generated using acetonitrile as solvent in the working range of 1-100 μ g/M,

Phatmacoldnetic parameters we e calculated using WiaNon-m software (4.1 version). Cim, Tmax, AUC 0-24, AUC O-Mnity, and Ty_2 characterized and each curve generated following oral treatment.

In Vitro Plasma stability;

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The rationale is that &e prodrugs would he hydr \mathbf{O} tyz $\beta \mathbf{d}$ in-vivo before, during or after absorption to release the cowespou $\delta i\pi \mathbf{g}$ free drugs. Therefore, we tested whether the test compounds (I-C1-NOPD6, 1-C1-NOPD4, I-C1-NOPD5A) released parent drug in rat plasma at 37 °C after 30 minutes incubation. The compounds were extracted back mto acetonitrile xvith rigorous vortex. The results suggested that all prodrugs tested except I-CI-NOPD6 were found to be converting to the expected metabolite (salicylate) of the parent drag (aspirin) as revealed by HPLC analysis. Even aspirin was completely metabolized to salicylate after 30 minutes of incubation with rat plasma indicating that all the teat compounds released aspirin, which in turn converted into salicylate.

Pharmacokinetic studies:

The oral pfcaπna<ttlάπetics of the test compounds, I-C1-NOPD6, I-CI-NOPD4, 1-C1-NOPD5A and 1-C1-NOPD5B was done in tats artd the release profiles of salicylate from these compounds were analyzed by HPLC and the results were presented in Figure I and Table 4. Overnight fasted rats were fed with 35 mg/kg equivalent doses of aspirin and test compounds. Blood was collected from orbital plexus of test animals at various time points up to 24 hrs. As shown in Figure U the test compounds I-C1-NOPD4 and I-C1-KOPD5B indicated unexpected drug release profiles wherein the salicylate is released in a sustained and controlled manner starling from 1 hour through 12 hours. For I-Cl-NOPJD5B, the plasma salicylate concentration was maintained between 50 and 75 μg/røl during this extended period of over 11 hours. This Jkind of plasma concentrations of the drag can result in significant extension of duration of action. For I-CJ-KOPD4 also, the plasma salicylate concentration was maintained between 35 and 50 μg/mL during aa extended period of over 11 hours. Although aspirin absorption (Figure 1) was highest during 0.5 - 6.0 hrs (during which period much of the damage to the gastrointestinal tract

of the subject occurs due to high concentrations of the drug), plasma salicylate concentration for aspirin and I-C1-NQPD4 were comparable during the period from 8 through 24 hours. Such sustained release profile of active drug frotft the prodrug is expected b cause negligible or insignificant gastrointestinal damage as the plasma concentration of the drug never reaches to the toxic levels. Similar release profile was observed with I-C1-N0PD5A but fox a shorter period of time. Unexpectedly, we have also observed as recorded in Table 4, nearly equal drug AUC values for aspirin and Ï-C1-NO3?D5B (Le., 923.63 ± 182,08 for aspwia vs 951-98 ± 11.58 for I-C1-NOPD5B) which indicates that the prodrug is as bioavailable as its parent drug, but prodrug does not cause gastric damage. Surprisingly, neither the prodrug nor the salicylate was found in the plasma of the animals fed with 1-C1-NOPD6 (data not included in the graph) at any point of time tested, the reasons for which are not Known.

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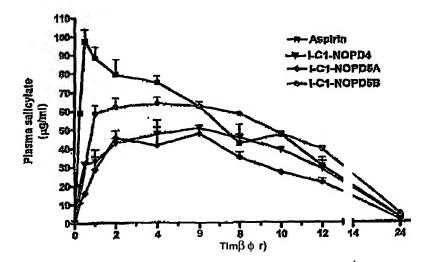


Figure 1. Plasma salicylate profile of aspirin and its NOrel βasing prodrugs, The data values at expressed as Mean * S_RM, a=3-4 animals, the data values at time points 6 and 10 hours is an average from two animals only.

Table4. CoDaaarison of pharaa &tøttetk parameters of aspirin and its nitro derivatives

parameter**	Afeptfn	I-CI -NPPD4	I.C1-NOPD5A	I-C1-NOPD5B
Cma* (μg Λπ L)	98.67 ±12.64	53.24 ±6.39	SD.14 ± 10.12	66,08 ±3.31
Tmax (h)	0.50 ± 0.00	4,66*0.57	3.00 i 0-57	4.00 ±0.81

AUC(MiH (h.μg/ml)	905.84 ± 173.14	749.36*69.38	557.80 ±97.65	922.89 ± 12.50
AUCm ₁ {h.μg/ml)	923.63 £ 182.08	772.17*75.68	565.30 ±96,78	951.98 ± 11.58
T _{1/2} (h)	3.58 ±0.42	3.984 0.25	3.35 ±0.32	4.14 ±0,24

^{*}Ti ie data values are mean \pm SEM, n^{β} 3-4

Ulcerogenic activity:

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Gastrointestinal ulceration is a serious side effect associated -with NSAIDs. The clinical uses of potent NSAIDs are greatly limited by its gastrointestinal toxicity. We tested ulcerogenic potential of the test compounds, KU-NOPD6, 1-C1-NOPD4, 1-C1-NOPD5A and X-CI-NOPD5B in tats. Overnight fasted rats were given orally 100 mgftg equivalent doges of aspirin and prodrugs (in the case of I-C1-NOPD5A and I-C1-NOPD5B, 200 mg/kg equivalent doses were administered). The animals were sacrificed at 3 hours after drug administration. Stomachs of treated rats ware separated, perfiised with IDml of 2 % formalin, and then cut open over the greater curvature. The severity of the tπopOsal damage was then assessed on the basils of size (area) of (he observed ulcers under surgical microscope with a square grid as per the established proc hdUfe (Takeuchi et al, J. Pharmacol. Exp. The*. 1998, 286 (1), 115-121), Interestingly, none of the animals treated vyith the test compounds showed any signs of development of ulcers. Howevet, severe hacmoxxhagic lesions (Mean * S.E.M.; 2,7 A 0.9 mm*) were seen ia aspirin, treated tats.

AntMirflaintt , atory activity:

Anti-inflammatory activity of test compounds was measured in carrageconaniaduced rat paw edema model (Tafeeuchi et al., J. Pharmacol. Exp. Ther. 1998, 286 (I) 9 U 5-121). The activity of aspirin and test compounds (75 mg/kg equivalent dose of aspirin) is shown *m* Table 5. Aspirin at 75 mg/kg, p.o. exhibited anti-iaflammatory activity from *I* hr through 6 hr with peak maximal activity at 4 hr. I-CI-NOPP4 showed significant activity during fltf first two hours after drug administration bm its activity was not as good as that of aspirin from 2 ht through 6 lit. Srapxismgly, I-C i-NOPDSA showed negligible ^-inflammatory activity at any time point tested (data not incorporated). We have not yet evaluated i-Cl-NOPD5B»n this efficacy test.

Table 5

Compound	Rat	t paw edema (% ii Mean* SEM	,	
	l honr	2 hour	4 hour	6hmr
Aspirin	31.0*7.2	52.5 ±3.4	60.7±6.9	42.8±6.9
I-C1-N0PD4	42.4 ± 13.3	44.9 ± 12.9	243 ±7.7	8.6±5.1

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The results indicate the following:

- I. Sustained release of the active drug over a period of 10-11 hows, which is good for twice daily dosage regimen, and
- 2. Exceptional gastrointestinal safety even at high equivalent doses of prodrugs compared b aspirin, which caused severe ulcers at equivalent doses.

We claim:

1. A compound of foxroula φ, novel intermediates in preparation thereof, or pharmaceutically acceptable salts thereof:

$$D^{1} \stackrel{L^{1}}{=} A \stackrel{A}{=} B \stackrel{A^{1}}{=} E \stackrel{L^{2}}{=} D^{2}$$
Formula (I)

wherein,

5

a is 0-2;

B jndependently represents a bond, (CHa)b, (CKbCH2O)0 S-S, S-S-O, S-SO2 or S-S=NH;

10 bis 1-6; c is MOOO;

A and A 1 independently represent a bond, (CH;_)«i, 1,2-phenylen $^\beta$, 1^-phenylenc or 1,4-phenyl $^\beta$ he;

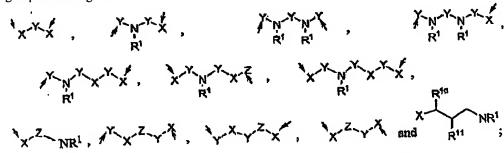
d is 1-8;

D¹ represents a therapeutic agpnt comprising one or more of the functional groups selected fitom the group consisting of -OH, -SH, -NHR¹, -COjH, -CONHR/, -OCC=O)KHR¹, -SO₂NHR¹, -OSO₂NHR^-N(Ry(O)NHR ¹ and -N(R¹JSOiNHR¹; D² independently represents P¹, a peptide, protein, monoclonal antibody, vitamin, R², R³, R⁴, NO, NOj, NONOate or any other nitric oxide-releasing group ormolecule, a group or molecule comprising one or mote of water-solubiltting functional groups, a polymer or

20 sn amino acid;

E independently represents CHj or a bond;

L¹ and I? independently represent a bond, O, S, NR¹, L, or a linkage selected &om the group consisting of:



L is R ¹² or a group with bonding in any direction, independently selected from the group consisting of;

X independently represents a bond, C, O, S, or NR Jj

- y independently represents a bond_> C=O, C=S, S=O, SO₂, P(O)XR⁻¹, or (CH[^]y, wherein ti is as defined;
 - Z independently represents a bond, or (CHj)Jj wherein.] is 1-4;
 - R¹ independently represents a bon4 H, (Ci-Oøalkyl. substituted(CrC ₅)alkyl, (Cj-Ci4)aryl, aralkyl or M*¹;
- 10 R² independency represents H₃NH?, or NHAc;
 - R³ independently represents H, CO₂R⁵ Or CHaCO₂R⁵;
 - R^4 independently represents H_7 OH, O-(Ci-C β alkyI, OM^* , or a group selected from the group consisting of:

$$CO_2R^6$$
, $CH_2CO_2R^6$, CO_2R^6 , CO_2R

M independently represents Na, K or a pharmaceutically acceptable metal ion;

5 e=1-3;

 R^5 independently represents at each occurrence H, M^{45} , (C_1-C_8) alkyl, (C_2-C_8) cycloalkyl, substituted (C_5-C_{14}) aryl, hetero (C_2-C_{14}) aryl, $C(=0)(CH_2)_fCHR^9CO_2R^5$, $CH_2C(=0)OR^5$, $P(=0)(OR^5)_2$,

10 X² independently represents O, S, SO, SO₂, or NR⁵;

 R^6 independently represents H, Na^+ , K^+ or any other pharmaceutically acceptable metal ion, (C_1-C_8) alkyl, or (C_3-C_8) cycloalkyl;

 R^{7} independently represents at each occurrence same or different R^{7} ;

R⁸ independently represents CH2, O, NR⁴, S, S=O or O=S=O;

15 R⁹ independently represents H, (C₁-C₈)alkyl or an amino acid;

f is 0-6;

g is 0-1;

h is 1-2000;

i is 1-4;

 R^{10} and R^{11} independently represent H, (Ct-Cs)aikyt, {C₃-Cg)cycloalkyl, or a group selected from ths group consisting of:

with a proviso that when R^{10} is selected from the above group, R^n represents H or $(C_r C_g)$ alfcyl, and when R^n is selected from the above group, R^{10} represents H or $(C_j - C_g)$ a3kyl;

R¹² independently represents a group selected from the group consisting of:

2. The compound according to claim 1, wherein a is 0.

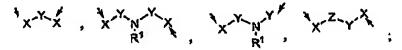
- 3. The compound according to claim % wherem D2 is a group or molecule comprising one or more water solubiHsing functional groups selected from the group consisting of hydroxy., amino, acylamino, carboxyï, sulphate, sulfonate, phosphate, püosphonat β, N-acylsulfonamide, N-acylsulfemate, N-acylcarbat Cate, N-acylcarbainate metallic salts* and amino acids to form, water-soluble prodrugs.
- The compound according to claim 2, wherein D² is selected from the group of amino acids consisting of Alanine, Argiøine Asparagi Te, Aspart io acid, Cysteine, Glut-unine, Glutamic acid, Glycine Histidine, Isoleiiciae, Leucine, Lysine, Methionine, Phenylalanine, Proline[^] Serine, Threonine, Tryptophan, Tyrosine, and Valine.
- 10 5. The compound according to claim 2 wh β rein D^2 is a polymer.
 - 6. The compound according to claim %wherein the polymer is selected from the group consisting of dejtfran, modified dextran, arabinogalactan, polyamiwo adds, and polyethylene glycol
- The compound according to claim 6, wherein the polymer is a polyaminoacid selected from group consisting of poly(l-gluta πύc acid), poly(d-glutamic acid), poly(dl-,15 gltitamic acid), poly(!-aspartic acid), poly(d-aspaitic acid), poly(dl- aspartic acid), copolymers of the polyaminoacids and polye%lene glycol, polycaprolaotoixe, polyglycolic acid, polylaclic acid, polyaciylic acid, polyc«t-ttydroxye%l 1-glutamine), dejctran aldehyde, carboxymethyl dextran, arabinogalactane aldehyde, carboxymetihyl atabi Üiogalactatte, and hyaluronic acid.
 - 8. The compound according to Claim 5, wherein the polymer has a molecular weight of about 5000 to about 100,000 Daltofls.
 - 9. The compound according to Claim 5, wherewi the polymet has a molecular iveight of about 10,000 to about 50,000 Daltons.
- The compound according to claim 2 wherein D² is a dipeptide. 25 10.

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The compound according to claim 2, wherein D1 is a vitamin selected from the 11. group consisting of Vitamin A, vitamin C, thiamine, folic acjd, Hotin, inositol, nicotinic acid, nicotinamide, riboflavin, pytidox ine, pyridoxa! 5-pb.osphate, ergostcrol, vitammP2j vitamin D3, vitamin D4, vitamin E, menadoxime, mena 6M, aad vitamin K5.

12, The coiapcmnd, according to claim 2, L^z is 0; A and A' are independently (CH[^] U-pheaylsro, U-phenylone* or 1,4-phenylone; d is 1-4; B is S-S, S-S=O₅ S-SO₂ or S-S=NH; D² is NO, NO_a or a NONOate selected from the group consisting of:

5 13. The compound according to claim 2, wherein L² is O; A and A¹ are CH2; E is CH₂; B is a bond or (CHa)1; b is 1-6; a is O; D² is NO* and L¹ is a group selected \(\text{\$\tilde{C}\$} \)om



wherein, X is O, S ox $W \ddot{I}$; and Y and Z are as defined.

14. The compound according to claim 2, selected front the group consisting of:

- 15. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 2, or a pharmaceutical salt thereof and one ox *mote* pharmaceutically acceptable carriers, vehicles or diluents.
- 16. A pharmaceutical composition comprising a therapeutically effective amount of
 the compound of claim 14, or a pharmaceutical salt thereof and one or more
 pharmaceutically acceptable carriers, vehicles or diluents.
 - 17. The compound as \hat{w} claim 2, wherein D¹ and D* represent known and investigational amino-, hydroxyl-, carboxyl-, and keto- containing drugs compiled in drug databases comprising the Merck index, $\hat{I}Ddb$, Ptous Science's Integrity[®], Prous Science Drugs of the FutoeTM, and The Ensemble [®].

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- The composition of claim 15 comprising therapeutically effective amount of pairs IS. of drugs selected from; paclitaxei and Doxorubicin; Paclitaxel and Mitomycin. C; 3-Aminopyridi πe-2-caγρογald hy<ie **Paclitaxel** and P-aminoce-mptotheciti; thjoseraicarbazon Ó 3-Arnkop3^dhe4 methyl-2-cafboxaldehyde (3-AP),thiosemicarbazofle (3-AMP) and Paclitaxel, Doxorubicin, WStomj'n C; CC-1065 and 15 Paclitaxel, Doxorubicin, Mitomycin C; Tra 78-Resv Bratrol ((E)-3,^5-tohydr Oxystilbet*e) and Paclitaxel, Doxorubicin, Mitomycin C; Retinoic acid and Butyric acid; Paclitaxd -md, Qaptopiil; Doxorubicin and Biotin; 5-Fko Towa α l and Cytarabi π e; Edatrexate and Pactitaxel; Cephalospojaaic acid rød PaclitaxeU Cephalosporin and PacUtaxelj PacÜtaxd and Oemcitatntt & Levodopa and Caibidopa; Amoxicillin and ClavuLanic acid; Ampicillm 20 and Clavulanic acid; Amoxicillin and Pencillinic add suJfon Ampidllk and PencHlittic acid sulfonic; Olivame acid and 3-substuuted Z-2-acylaminopiopi θ_{EM} acid; Liflbrol and Lovastatir^Prav^atin/F^^ tetin/Atorvastatin/Simvastatin; Ezetiwib β and Lovastatin/ Pravastatin/ Fluvastatin/Atofvastalin/Sinivastalin; Amtodipine and L^vflstatin/Pr v_istat-M/H^ astatin/Atorvastatin/Simvastatin; Metfo π nin and 25 Nateglinide/Glipizide/Glibejiclamide (Glybuxide); Metformin and Lo Atattø/Pravastatir V πuv^^ in/Atorvastatin/Simvastatin; Pseudoephedrine Salbuta Tool and Ipratropium bicomid & F^ofenadrae/Cetirizine^esloirøtadke/EpinastJne; Mometasone and Foκenerterol/5al)r@terøl; Flutiicasoiiβ and Fownoterol/Salnifet@ol;
 - Budesotdde and Fomioterot/Salmeterol; Diclofenac and Misoprostol; Diclofenac and Omeo azole/Usopjfl-Ml/ beprazole/Leminoprazole/Pentoprazole; Naproxen and

Acetaminophen and chloxzoxazone/ftnetaxalone/røeph@noxalone; Prophenazonc; Zidovudine and JLaimvudine; Triple prodrug of Zidovudine; Lamivudine and Abacavir (Ziagen); Lopinavir and Ritonavir; Lamivudme and Adefovir/dipjvox Ü; Amprenavix and Zidovudine: Nelfinavir and Zidovudine/Lamivudine: Stavudine Zidovudine/Laraivudine; Dideoxyinosine and Zidovudine/Laraivudi αβ; Emtricitabine and Pe&ciclovfr/Famciclovk; Acyclovir and dβoxycholate/chenodcoxycholate and ursodeoxycholat β Triple and Zidovudine; and Lamivadinc and Efevire π z.

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- 19, A therapeutically effective amount of the pharmaceutical composition as in claim 15, comprising a two ox ∞ or β drugs, a drug and its own prodrug, a drug and a different prodrug, two different prodrugs, a drug and a mutual prodrug, mutual prodrug and its own drugs or a mutual prodrug and one of its constituent drugs.
- The compound according to claim 2, wherein D1 and D2 are therapeutic agents 20. selected from the group consisting of: Sedatives, Hypnotics, Antidepressants, Antipsychotics and Antimanics, Analgesics, Antipyretics, Antimigraine 15 Anticonvulsants, Drugs used in parkinsonism and movement disorders, Drug for dementia, Antiemtics, drugs for Vertigo, CNS Stimulants activators; Antiinfective eye preparations; Antiinflammatory; antiallergic preparations, a Otiglucoma preparations to cure eya diseases; aural, nasal and oropharyngeal preparation, Antaaπihythemic drugs, Antihypertensives,, alfa/beta-olockers, channel blockers, ACE 20 inhibitors, Angiotensin II receptor antagonist[^] diuretics. Antianginals* nitrates, calcium channel blocker' Drags for cardiac Mure and shock, Vasodilators, Coagulants, Anticoagulants, Thrombolytics, antiplatelet drugs, Respiratory stimulants, Antitissives, Expectorants, Mucolytics, Decongestants, Antihistamine agents, antiwihmaticg; Antiulcer, Antisecretory drugs, H_i> receptor aratagonists, Pioton Pump ϊίπhibitors, 25 Prostaglandin analogues, Antacids, Antispasmodics, drugs modifying intestinal motility, Antidianrhoeals, antimotility drugs, antimicrobial drugs, drugs acting on gall bladder, Urinary antunfectives, Piuretics, Urinary analgesics, Antispasmodics, Antiinfective drugs acting on urethra and vagina, drugs acting on uterus, Drugs for prostatic hypertrophy, alfa blockers, antiaπdrogens, Drugs for erectile dysfunction, Spermicidals, nonhormonal contraceptives, Emollients, keratolyt.es, topical affliinfectives, topical 30 antifungals, topical paiasitiddals, topical steroids, topical drugs for acne vulgaris, ≮rugs

for psoriasis, pigmentation disorders, and Antiseboirrhoeics, Non Steroidal Anti Inflammatory Drugs (NSAIDs), COX-2 inhibitors, Anriarfhritic agents, Immunosuppressants, Topical analgesics, Muscle relaxants, Neuromuscular Drugs, Penicillin antibiotics, Cephalosporin antibiotics, Quiπolone, Fluoroquinolone antibiotics, MacroUde antibiotics, Chloramphenicol, Tetracyline antibiotics, 5 Antiatiaerobics, Metronidazole, Antitubercular drugs, Antileprosy drugs, Antifungals, Antiprotozoals, Anthelrainthics, Anti infesiive Drugs, Antimalarials, Antivirals, Anabolics, androgenic steroids, Corticosteroids, Oestrog βns, Progestogens and Hoπnonal contraceptives. Fertility Agents, Trophic hormones and related drugs, Thyroid and antithyroid drugs, Antidiabetics and hyperglycemics, Vitamins, Amino acids, Anti-10 obesity drugs, HypoHpidaemic drugs, fibric acid derivatives, statins, HMG CoA reductase inhibitors* nicotinic acid group, drugs used for Gout, drugs affecting bone metabolism, bisphosphonates, Anticancer drugs, alkylating agents, cytotoxic antibiotics, antimetabolites, cytarbine, Fhidarbine, 5»Fluorouracil, Mercaptopurine, Thioguanine, Topois Omerase 1 inhibitors, Cytotoxic 15 Vinca alkaloids, Etoposide, Taxancs, Cytoprotectives, Oestroge π s, immunosuppressants, Immunostmulants, Amifostine, Progestogens, hormon antagonists, antineoplastic drugs, Antiallurgics, non-sedattve antibista π ims, Cetirizin β D β 0 loratadine, Terfenadine, Fescofenadine, sedative histamines, histamine receptor blockers, Local anaesthetics, intravenous anaesthetics, inhalation **2**Q anaesthetics, and muscle relaxants.

- 21. The compound according $^{\circ}$ 0 claim $^{\circ}$ 6 wherein D^{1} and $D^{^{\circ}}$ ate from same or different therapeutic class and exhibit either the same or different mechanisms of action or wttJc on same or different biological targets or -work on same or different disease conditions.
- 25 22. A method of treating a mammal or human in F βed thereof comprising administering a therapeutically effective amount of the composition according to claim 15.
 - 23, A method of treating a mammal or human in need thereof comprising administering a therapeutically effective amount of the coirφostøon according to claim

30 16.

- 24. A method of use of the compound according b claim 2, for prevention or treatment of diseases where a chronic, sustained and selective release of the constituent drug Q nitric ojude is beneficial.
- 25. A method of use of the compound according to claim 2, iα subject in need there of for prevention or treatment of diseases of Central Nervous System, Eye, Ear, Nose and Otophatyπx, Cardiovascular System, Respiratory System, Gastrointestinal tract system, Gemito-urinary system, skin, musculoskeletal system, Bodocrine system, metabolism and neoplastic disorders, infectious diseases, allergy and immunology, and for anaesthetic, analgesic and surgical needs.
- 10 26. A method of testing a mammal or human In need thereof comprising administering a iheiapeutically effective amount of two or more compositions according to claim 15, wherein compositions used in combination to treat a patient in need of a combination therapy.
- 27. A method of use of composition as claimed in claim 15, for prevention and/or
 15 treatment of diseases where a chronic sustained and selective release of the constituent drag(s) and/or πitoie oxide ig beneficial.
 - 28. The novel mtemtediates obtained in the preparation of compounds of dajra 1, wherein the intermediates are selected from:

2-((2-Hydroxyethyl)disulfanyl)ethyl acetate (LI-1a)

2-((2-(Trityloxy)ethyl)disulfanyl)cthanol (LI-1e)

2-((2-Hydroxyethyl)disulfanyl)-ethyl nitrate (LI-2b)

2-((2-Hydroxycthyl)disulfanyl)ethyl nitrate (LI-2c.TFA)

terr-Butyl 2-((2-bromoethyl)-disulfanyl)ethylcarbamato (LI-2e)

1,2-Bis(2-bromeethyl)disulfane (LI-3a)

2-((2-Aminoethyl)disulfanyl)ethyl nitrate, acid salt (LI-5.TPA)

2-((2-(Tetrahydro-2//-pyran-2-yloxy)ethyl)disulfanyl)ethanol (LI-1b)

2-((2-Hydroxyethyl)disulfanyl)ethyl 2-chloroacetate (LI-1d)

2-((2-Bromoethyl)disulfanyl)ethanol (LJ-2a)

tert-Butyl 2-((2-hydroxyethyl)disulfanyl)ethylcarbamate (LI-2c)

2-((2-(tert-Butoxycarbonylamino)ethyl)-disnifanyl)ethyl methanesulfonate (LI-2d)

tert-Butyl 2-((2-(nitrooxy)ethyl)-disulfaryl)ethylcarbamate (LI-21)

2,2'-Disulfanediylbis(ethane-2,1-diyl) dinitrate (LI-3b)

2-((2-Aminoethy))disulfanyl)ethyl nitrate (LI-5)

2-((2-Bromoethyl)disulfanyl)ethyl carbonochloridate (LI-6)

- 29. The use of the novel intermediates of claim 28, in the preparation of compounds of formula i or phawnaceutically acceptable salts thereof,
- 5 30. Tlicprociessforlii βï n^OTatiottofthccompoi ωdasin^a ïa l^cffa phaππaceutically acceptable salts thereof, wherein the process is selected from: Process 1: A) Monoprotection of Bis-(2-hydroxyethyl)disulphide (SL-I) with an appropriate bydioxyl protecting group to give the corresponding moQoprotected intermediate LMx,

2-((2-((2,5-Dioxopyrrolidin-1-yloxy)carbonyloxy)ethyl)-disulfanyl)ethyl 2-(dimethylamino)ethylcarbamate (LI-10)

10 B) Converting LHx, obtained in step A to an activated formyl intermediate Ll-Ixy by treating wifh phosgene ox its equivalent, and

- C) Reacting $JJ \Lambda xy$ obtained in the step B with an appropriate amino* or hydroxyl contahkig drug (D¹) to give the corresponding compound of formula I;
- Process 2: A) Converting carboxyl containing drug (J)) into its activated acyl halide or imidazolide or is α yajiate by k β own methods, and
- 5 B) Reacting the inteπnediate obtained in the step A with the linker intermediate LI-Ix to obtain the compound of formula i;
 - Process 3: Mixing a selectively protected and activated drug with a solution of 2-((2-hydroxyethyl)dittiio)ethyl nitrate (Lï-2b) in a suitable solvent in presence of a suitable coupling agent to obtain the compound of formula I andphannaceutically acceptable salt
- 10 tiiereof, wherein D² is NCtø
 - Process 4: Converting 2-((2-hydroxye%l)di*hio)ethyl nitrate (LI-2b) into its formyl halide or hnidaaolide (LI-4 χ) by using a phosgene or its equivalent reagent and mixing/reacting the resulting reactive intermediate with a suitable amino- or hydroxycontainifig drug in suitable solvent in presence of a suitable base to obtain the compound
- of formula I and pharmaceutically acceptable salt thereof > wherein Da is NO^;
 - Process 5: Mixing/Fcacting an appropriately protected and activated drag with a solution of 2-((2-aminoethyI)dithio) β hyl nitrate (LI-5) in a suitable solvent in presence of a suitable coupling agent and/or base to obtain the compound of formula I and phatmaceutically acceptable salt thereof, whei ϕ n D² is NO₂; and
- 20 Process 6: A) Monopirotection of Bis-(2-h.ydToxye1hyl)disulphide (SL-l) with an appropriate hydroxyl protecting group to give the corresponditty monoprotected intermediate LMx,
 - B) Reacting formyl linker tate π nediatell-lxy with amiao or hydi \mathbf{G} xyl containing drug (D¹) to obtain the prodrug of formula I with free hydroxyl group on the linker,
- 25 C) Converting the intermediate obtained in the step B into activated formyl halïde or imidazolide derivative, aft4
 - D) Reacting the intermediate obtained in the step C with the drug P^2 to obtain the mutual prodrug of formula L

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Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i))
- as to applicant's entitlement to apply for and be granted a
 patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PRODRUGS AND CODRUGS CONTAINING BIO- CLEAVABLE DISULFIDE LINKERS

(57) Abstract: The invention provides the compounds of formula (I) or pharmaceutically acceptable salts thereof. The invention also provides pharmaceutical compositions comprising one or more compounds of formula (I) or intermediates thereof and one more of pharmaceutically acceptable carriers, vehicles or diluents. The invention further provides methods of preparation and methods of use of prodrugs including NO-releasing prodrugs, double prodrugs and mutual prodrugs comprising the compounds of formula (I).



INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER INV. A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

 $\begin{tabular}{ll} Minimum documentation searched (classification system followed by classification symbols) \\ A61K \end{tabular}$

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS

			Relevant to claim No.
Category*	Citation of document, with indication, where appropriate, of the	e relevant passages	Helevant to dailit No.
х	WO 03/040104 A (BIOTA SCIENTIF MANAGEMENT PTY LTD; JIN, BETTY JOHN, N; NEA) 15 May 2003 (200 pag. 6 lines 7-12; pag. 45 str	; LAMBERT, 03-05-15)	1-3,20, 21
x Y	WO 2004/039771 A (DEPARTMENT O AND TECHNOLOGY; TIWARI, MANISH MEENAKS) 13 May 2004 (2004-05- Comp. II pag. 4;	A; SHARMA,	28 1-3, 14-16,
			18-30
x	US 2003/044845 A1 (JENKINS THO 6 March 2003 (2003-03-06)	MAS E ET AL)	1
γ	Abstract, Example A44 pag. 106	;	1-3, 14-16, 18-30
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X Furth	ner documents are listed in the continuation of Box C.	X See patent family annex.	
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filing d L* docume which i	nt which may throw doubts on priority claim(s) or s cited to establish the publication date of another	"X" document of particular relevance; the cl cannot be considered novel or cannot involve an inventive step when the doc "Y" document of particular relevance; the cl	be considered to cument is taken alone calmed invention
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lame and m	nailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,	Authorized öfficer Bettio, Andrea	

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/052797

Catagory' Citation of document, with indication, where appropriate, of the relevant passages X	
AND CARDIOVASCULAR AGENTS MODULATING THE BIOACTIVITY OF NITRIC OXIDE" CIRCULATION RESEARCH, GRUNE AND STRATTON, BALTIMORE, US, vol. 90, no. 1, 11 January 2002 (2002-01-11), pages 21-28, XP008051659 ISSN: 0009-7330 cited in the application Fig. 5 pag. 24 P,X SHARMA M ET AL: "Bis[3-(4'-substituted phenyl)prop-2-ene]disulfides as a new class of antihyperlipidemic compounds" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 14, no. 21, 1 November 2004 (2004-11-01), pages 5347-5350, XP004580528 ISSN: 0960-894X Pag. 5348 Scheme 1 comp. 6 Y WO 2004/069159 A (ENDOCYTE, INC; VLAHOV, IONTCHO, RADOSLAVOV; LEAMON, CHRISTOPHER, PAUL;) 19 August 2004 (2004-08-19) Pag. 81 Example 37 and 38 Y US 6 566 509 BI (GRIFFIN JOHN H ET AL) 20 May 2003 (2003-05-20) Columns 45 structure X3; column 95 structure X 381 P,Y US 2005/002942 A1 (VLAHOV IONTCHO R ET AL) 6 January 2005 (2005-01-06) cited in the application Example 37 pag. 60 Y MAHGOUB H ET AL.: "Spectrophotometric determination of binary mixtures of pseudoephedrine with some H1-receptor antagonists using derivative ratio spectrum method" JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS, vol. 31, 2003, pages 801-809, XP002393773 Abstract, pag. 802 last parpag 805 second column par. 2 A WO 01/13957 A (CELLGATE, INC)	Relevant to claim No.
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Claim 73; Pag. 36 lines 24-31	1-3, 14-16, 18-30

International application No. PCT/IB2005/052797

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: 17 because they relate to subject matter not required to be searched by this Authority, namely: see FURTHER INFORMATION sheet PCT/ISA/210
2. X Claims Nos.: 17 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically: See FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
see additional sheet
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely pald by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. X No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-3, 14-16, 18-30 in part
Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

Continuation of Box II.1

Although claims 22-27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition. Although claims are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 17

The present claim 17 relates to an extremely large number of possible compounds. The non-compliance with the substantive provisions is to such an extent, that no search was performed (PCT guidelines 9.01).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-3, 14-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 and D2 are both independently selected from Cetirizine, Desloratadine, Terfenadine and Fexofenadine and Pseudoephedrine; except for the subject matter of inventions 2-24

2. claims: 1-3, 14-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 and D2 are both independently selected from Lisinopril, Losartan and Amlodipine; except for the subject matter of inventions 1, 3-24

3. claims: 1-3, 14-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 and D2 are both independently selected from Celecoxib and Valdecoxib; except for the subject matter of inventions 1, 2, 4-24

4. claims: 1-3, 14-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 and D2 are both selected independently from Fluoxetine and Olanzapine; except for the subject matter of inventions 1-3, 5-24

5. claims: 1-3, 11, 14-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 and D2 are both independently selected from Gabapentin, Pregabalin, Vigabatrin, valproic acid, nicotinic acid, nicotinamide, Lamotrigin, Levetiracetam, Naproxen and Tramadol; except for the subject matter of inventions 1-4, 6-24

6. claims: 1-3, 14-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 and D2 are both independently selected from Lamivudine and Zidovudine; except for the subject matter of inventions 1-5, 7-24

7. claims: 1-3, 14-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 and D2 are both independentlyselected from Metronidazole and Norfloxacin; except for the subject matter of inventions 1-6, 8-24

8. claims: 1-3, 14-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 and D2 are both independently selected from Venlafaxine and Paroxetine; except for the subject matter of inventions 1-7, 9-24

9. claims: 1-3, 15, 18-30 in part; claim 11 complete

Conjugates embraced by formula (I) of present claim 1 wherein D2 is a vitamin selected from the group consisting of vitamin A, vitamin C, thiamine, folic acid, biotin, inositol, riboflavin, pyridoxine, pyridoxal 5-phosphate, ergosterol, vitamin D2, vitamin D3, vitamin D4, vitamin E, menadoxime, menadiol, and vitamin K5; except for the subject matter of inventions 1-8, 10-24

10. claims: 1, 2, 14-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D2 is R2 and R2 independently represents H, NH2, NHAc; except for the subject matter of inventions 1-19, 12-24

11. claims: 1, 2, 14-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D2 is R2 and R2 independently represents COR5 or CH2CO2R5 and wherein R5 is defined as in present claim 1; except for the subject matter of inventions 1-10, 12-24

12. claims: 1, 2, 12-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D2 is R4 and R4 represents one of the groups defined in present claim 1 except H, amino-functionalised water soluble polymers and except amino-modified dextran or arabinogalactan; except for the subject matter of inventions 1-11, 13-24

13. claims: 1, 2, 12-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 is selected from Gabapentin, Pregabalin, Vigabatrin, valproic acid, nicotinic acid, nicotinamide, Levetiracetam, Lamotrigin and D2 is NO, NO2 or NONOate; except for the subject matter of inventions 1-12, 14-24

14. claims: 1, 2, 12-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 is selected from Lisinopril, Hydralazine, Amlodipine and D2 is NO, NO2 or NONOate; except for the subject matter of inventions 1-13, 15-24

15. claims: 1, 2, 12-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 is selected from Omeprazole, Metronidazole and D2 is NO, NO2 or NONOate; except for the subject matter of inventions 1-14, 16-24

16. claims: 1, 2, 12-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 is selected from Valdecoxib and Celecoxib and D2 is NO, NO2 or NONOate; except for the subject matter of inventions 1-15, 17-24

17. claims: 1, 2, 12-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 is selected from Paracetamol and Aspirin and D2 is NO, NO2 or NONOate; except for the subject matter of inventions 1-16, 18-24

18. claims: 1, 2, 12-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 is 1-hydroxy-TEMPO and D2 is NO, NO2 or NONOate; except for the subject matter of inventions 1-17, 19-24

19. claims: 1, 2, 12-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 is Budenoside and D2 is NO, NO2 or NONOate; except for the subject matter of inventions 1-18, 20-24

20. claims: 1, 2, 12-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 is selected from Naproxen, Flurbiprofen, Indomethacin, Ketoprofen, Diclofenac and D2 is NO, NO2 or NONOate; except for the subject matter of inventions 1-19, 21-24

21. claims: 1, 2, 5-9, 15, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D2 is a polymer selected among dextran, modified dextran and arabinogalactan; except for the subject matter of inventions 1-20, 22-24

22. claims: 1, 2, 5-9, 15, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D2 is a polyaminoacid; except for the subject matter of inventions 1-21, 23, 24

23. claims: 1, 2, 5-9, 15, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D2 is polyethylene glycole (PEG); except for the subject matter of inventions 1-22, 24

24. claims: 1, 2, 15, 18-30 in part 4; 10 complete

Conjugates embraced by formula (I) of present claim 1 wherein D2 is an amino acid selected among those disclosed in present claim 4 or a dipeptide; except for the subject matter of inventions 1-23

INTERNATIONAL SEARCH REPORT

International application No PCT/IB2005/052797

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